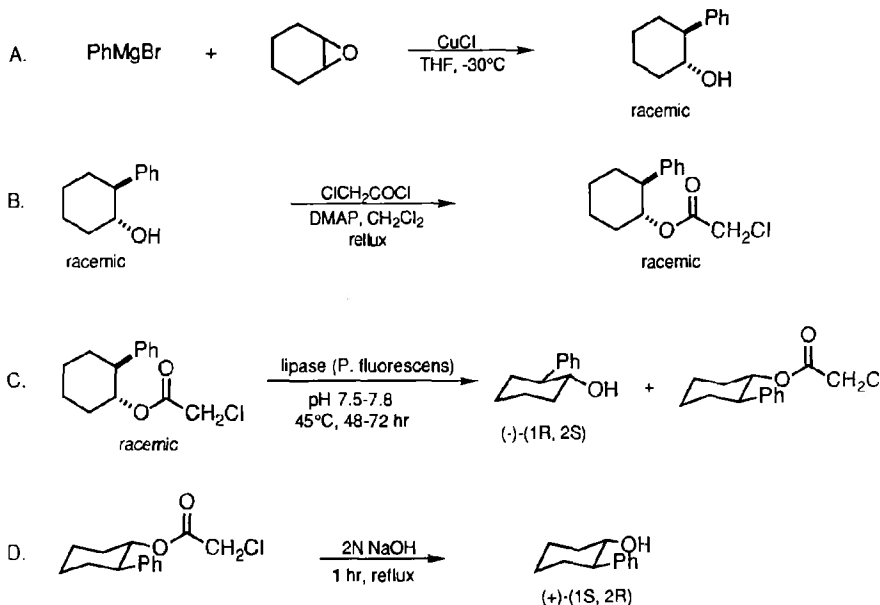


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**LIPASE-CATALYZED KINETIC RESOLUTION OF ALCOHOLS VIA
CHLOROACETATE ESTERS: (-)-(1R,2S)-trans-2-
PHENYLCYCLOHEXANOL AND (+)-(1S,2R)-trans-2-
PHENYLCYCLOHEXANOL**

(Cyclohexanol, 2-phenyl-, (1R-trans)- and cyclohexanol, 2-phenyl-,
(1S-trans)-)



Submitted by A. Schwartz,¹ P. Madan,¹ J. K. Whitesell,² and R. M. Lawrence.²

Checked by Robert E. Maleczka, Jr. and Leo A. Paquette.

1. Procedure

A. Racemic trans-2-phenylcyclohexanol. A 3-L, round-bottomed flask equipped with a mechanical stirrer, addition funnel, reflux condenser, and nitrogen inlet is charged with 35.3 g (1.47 g-atom) of magnesium turnings (Note 1) and 170 mL of dry tetrahydrofuran (THF). To this stirred mixture a solution of 155 mL (1.47 mol) of bromobenzene (Note 2) in 250 mL of dry THF is added dropwise over a 1.5-hr period (Notes 3 and 4). After the addition of bromobenzene is complete, 1 L of dry THF is added. The solution is cooled to -30°C (dry ice-nitromethane slush bath) and 6.53 g (0.066 mol) of purified (Note 5) copper(I) chloride is added. The resulting mixture is stirred for 10 min and then a solution of 101 mL (1.0 mol) of cyclohexene oxide (Note 6) in 100 mL of THF is added dropwise over a 1.5-hr period. Upon completion of the addition, the reaction mixture is allowed to warm to 0°C and stirred for 2 hr, then quenched by adding 500 mL of saturated ammonium sulfate $[(\text{NH}_4)_2\text{SO}_4]$ solution (aqueous). The layers are separated and the organic layer is washed with 100 mL of saturated $(\text{NH}_4)_2\text{SO}_4$ (Note 7). The combined aqueous layers are extracted with ether, the organic layers are combined and dried over anhydrous MgSO_4 , and the solvent is removed via rotary evaporator to give 175.5 g (99.6% crude) of the desired product as a light yellow solid. The solid is recrystallized from pentane to give 142.3 g (80%), mp $55.5\text{--}57.0^{\circ}\text{C}$ (lit.¹² $57\text{--}58^{\circ}\text{C}$) (Note 8).

B. Racemic trans-2-phenylcyclohexyl chloroacetate. A 1-L, round-bottomed flask equipped with a magnetic stirrer and a condenser is charged with 100 g (0.567 mol) of racemic trans-2-phenylcyclohexanol, 50 mL (0.625 mol) of chloroacetyl chloride (Note 9), 300 mg (0.0025 mol) of 4-dimethylaminopyridine (DMAP) (Note 10) and 250 mL of dichloromethane. This mixture is rapidly stirred and heated at reflux for 6 hr. The mixture is cooled and a solution of 350 mL of saturated sodium bicarbonate is carefully added to the rapidly stirring mixture (Note 11). Stirring is maintained for 3

hr (Note 12). The organic layer is separated and dried over anhydrous potassium carbonate. After filtration the filtrate is concentrated on a rotary evaporator (30°C) to a dark brown oil. This oil is distilled through a 2"- or 4"-column packed with glass beads to give, after collecting a small forerun (ca. 2 g), 135 g (94%) of racemic *trans*-2-phenylcyclohexyl chloroacetate as a colorless liquid, bp 118-122°C/0.3 mm.

C. (-)-(1*R*,2*S*)-*trans*-2-Phenylcyclohexanol. A 500-mL, three-necked Morton flask (Note 13) equipped with a mechanical stirrer, pH probe (connected to a pH controller, Note 14) and a base inlet (connected to a syringe pump regulated by the pH controller and a calibrated 250-mL reservoir (Note 15) of 1 N sodium hydroxide) is charged with 106.0 g (0.419 mol) of racemic *trans*-2-phenylcyclohexyl chloroacetate, 10 mL of pH 7 buffer (Note 16), and 90 mL of deionized water. This heterogeneous mixture is rapidly stirred and heated to between 45°C and 50°C using a constant temperature bath. The pH is adjusted to 7.5 with 1 N sodium hydroxide and after a steady pH reading is achieved (Note 17), 1 g of lipase (*P. fluorescens*, Note 18) is added. Immediately 1 N sodium hydroxide begins to flow into the reaction mixture as the pH begins to drop (indicating hydrolysis of the chloroacetate). The pH controller regulates the addition of base so as to maintain the pH between 7.5 and 7.8. After 2 hr, an additional 1.5 g of lipase is added to the reaction mixture and the rate of hydrolysis becomes noticeably faster (Note 19). After 45 hr, ~200 mL (~95% of theory) of 1 N sodium hydroxide has been added and the rate of hydrolysis has become very slow. After ~50 hr, 210 mL of 1 N sodium hydroxide (0.21 mol, 100% of theory) has been added to the mixture and the rate of base addition has nearly stopped (Note 20). The mixture is cooled to room temperature and extracted with three 200-mL portions of ether. The organic layer is filtered through a small pad of Celite to remove traces of enzyme emulsion and the Celite is rinsed with three 100-mL portions of ether. The combined organic layers are dried over anhydrous sodium sulfate and after filtration are concentrated on a rotary evaporator (35°C) and finally dried at 0.5 mm for 1 hr to

give 93 g of a colorless oil. Fractional crystallization from 100 mL of petroleum ether (30-60°C) at -20°C (freezer) overnight affords 19.8 g (53.5% of theory, Note 21) of (-)-(1R,2S)-trans-2-phenylcyclohexanol as colorless needles, mp 63-65°C, $[\alpha]_{\text{D}}^{25}$ -54.3° (methanol, *c* 18). An additional 15.8 g of the (-) alcohol is obtained by chromatography of the mother liquors (*vide infra*) to afford a total of 35.6 g (96.2% of theory, Notes 21 and 22).

The mother liquors are concentrated on a rotary evaporator (35°C) to give a colorless oil that is redissolved in 100 mL of hexanes and poured onto a 250-g pad of silica gel (Note 23) contained in a 500-mL sintered glass funnel, pre-equilibrated with hexanes. Using this simple silica pad, 100-mL fractions are collected, diluting first with 1 L of hexanes, followed by 3 L of 9:1 hexanes:ethyl acetate, and finally with 600 mL of ethyl acetate. After TLC analysis of the eluants (Note 24), fractions 3-18 are combined and concentrated initially on a rotary evaporator (40°C) and finally dried at 0.5 mm to afford 52.0 (98% of theory) of (-)-(1S,2R)-trans-2-phenylcyclohexyl chloroacetate as a colorless oil, $[\alpha]_{\text{D}}^{25}$ -14.3° (benzene, *c* 10). Fractions 20-28 are combined and concentrated as above to afford 15.8 g of the (-)-(1R,2S)-trans-2-phenylcyclohexanol, mp 62-65°C, $[\alpha]_{\text{D}}^{25}$ -54.9° (methanol, *c* 2.1).

D. (+)-(1S,2R)-trans-2-Phenylcyclohexanol. A 500-mL, round-bottomed flask is charged with a mixture of 52.0 g (0.206 mol) of (+)-(1S,2R)-trans-2-phenylcyclohexyl chloroacetate, 250 mL of 2 N sodium hydroxide, and 100 mL of methanol and then stirred at reflux for 3 hr. TLC analysis (Note 24) indicates complete reaction. The mixture is cooled to room temperature, adjusted to pH 7 with ~35 mL of 3 N sulfuric acid and poured into 500 mL of water. The mixture is extracted with two 150-mL portions of dichloromethane and the organic layer is dried over anhydrous sodium sulfate and concentrated on a rotary evaporator (35°C) to afford 37.0 g of a colorless solid. Recrystallization from 100 mL of petroleum ether (30-60°C) at -20°C gives in

two crops, 35.8 g (96% of theory) of (+)-(1S,2R)-trans-2-phenylcyclohexanol as colorless needles, mp 60-62°C, $[\alpha]_D^{25} +52.8^\circ$ (methanol, c 5.4) (Note 25).

2. Notes

1. Magnesium turnings were purchased from Aldrich Chemical Company, Inc.
2. Bromobenzene was purchased from Fisher Scientific and used without further purification.
3. A small amount of 1,2-dibromoethane was used to initiate the reaction.
4. An ice bath was used to control the reaction temperature during Grignard formation.
5. Copper(I) chloride was purified via the procedure in *Inorganic Syntheses*.³
6. Cyclohexene oxide was purchased from Aldrich Chemical Company, Inc. and used without further purification.
7. The organic layer was washed until the aqueous layer no longer turned blue.
8. The spectral properties of the product are as follows: ¹H NMR (300 MHz) δ : 1.25-1.53 (bm, 4 H), 1.62 (s, 1 H), 1.76 (m, 1 H), 1.84 (m, 2 H), 2.11 (m, 1 H), 2.42 (ddd, 1 H, J = 16.5, 10.8, 5.4), 3.64 (ddd, 1 H, J = 10.8, 10.8, 5.4) 7.17-7.35 (m, 5 H); ¹³C NMR (90 MHz) δ : 25.1 (t), 26.1 (t), 33.5 (t), 34.7 (t), 53.0 (d), 74.0 (d), 126.4 (d), 127.9 (d), 128.4 (d), 143.8 (s); IR cm⁻¹: 3592, 3461, 2941, 2863, 1604, 1497, 1451; MS 176 (M⁺), 158, 143, 130, 117, 104, 91 (base).
9. Chloroacetyl chloride (99%) was purchased from Fluka and used without further purification.
10. 4-Dimethylaminopyridine was purchased from the Aldrich Chemical Company, Inc., and used without further purification.

11. Rapid addition of the bicarbonate solution may result in uncontrollable foaming.

12. Excess chloroacetyl chloride was slowly hydrolyzed to chloroacetic acid which was neutralized.

13. A creased or Morton flask was preferable as the rate of hydrolysis of the chloroacetate increases with efficient agitation.

14. The pH controller used was a Horizon Model 5997 available from Cole-Parmer Instrument Co.

15. A 250-mL graduated cylinder, used as a reservoir, was capped with a septum through which base-stable, 1/32"-I.D. tubing was run and connected to a peristaltic pump.

16. Fisher pH 7 buffer was used from the bottle as purchased.

17. Traces of chloroacetyl chloride are hydrolyzed to produce chloroacetic acid, producing a fluctuation in pH that will settle down within 5 min.

18. The lipase used was isolated from *Pseudomonas fluorescens* and was commercially available from Amano International Enzyme Co., Inc. (Troy, VA) as a powder, specific activity 32,000 units/g (P-30).

19. The rate enhancement was manifested by a more rapid base uptake.

20. If the hydrolysis was allowed to proceed, small additions of base (0.1 mL or less) occurred every 30 min or so.

21. If the hydrolysis was taken to 50% completion, the theoretical yield of each alcohol isomer was 36.96 g.

22. The (-)-(1R,2S) alcohol had an enantiomeric ratio of (-):(+) 99.2:0.8 corresponding to an enantiomeric excess (ee) of 98.4%. This determination resulted from GC analysis (50 m x 0.25 mm capillary column, OV-17 on fused silica, 250°C) of the α -methoxy- α -trifluoromethylphenylacetate (MTPA ester). The checkers determined the enantiomeric ratio to be 98.6:1.4 (97.2% ee) by ¹H NMR analysis at

300 MHz of the MTPA ester that was prepared as follows: The sample alcohol (0.1 mmol) was placed in a vial along with a solution of (+)- α -methoxy- α -trifluoromethylphenylacetyl chloride (0.15 mmol) in 1 mL of dichloromethane, triethylamine (0.15 mmol), and a crystal of 4-dimethylaminopyridine, and stirred at room temperature overnight. The excess acid chloride was treated with dimethylaminopropylamine (0.1 mmol). The MTPA ester was isolated in pure form after passing the mixture through a 5-g plug of silica gel and elution with 4:1 hexanes:ethyl acetate.

23. The silica gel used was 70-230 mesh as purchased from E. Merck.

24. TLC was run on 10 x 20-mm silica plates (E. Merck): TLC solvent was 4:1 hexanes:ethyl acetate; visualization was with 5% $(\text{NH}_4)_2\text{MoO}_4$ in 10% aqueous sulfuric acid, with heat. In the event that any mixed fractions are obtained, these are combined, evaporated, and the residue is rechromatographed in the same manner.

25. By GC analysis of (+)-MTPA esters (see Note 22), an enantiomeric ratio of (+):(-) 96.5:3.5, corresponding to 93% ee, was determined.

3. Discussion

The use of chiral auxiliaries to impart dissymmetry has become a powerful tool for controlling the stereochemical outcome of chemical transformations. Many of these auxiliaries have been drawn from the chiral pool of natural materials. While high levels of asymmetric induction have been achieved in many cases, none of these natural products has emerged as a general agent, in part because typically only one enantiomer of the auxiliary is readily available.

The procedure described here provides ready access to both the (+)- and (-) antipodes of trans-2-phenylcyclohexanol, a useful chiral auxiliary in ene reactions of its glyoxylate ester⁴ and its N-sulfinylcarbamate,⁵ as well as in cycloaddition reactions

of dienes with the N-sulfinylcarbamate,⁶ and olefins with ketenes.⁷ This simple auxiliary appears to retain⁴ many of the features of 8-phenylmenthol,⁸ a powerful agent difficult to prepare on a large scale.⁹ A modest-scale procedure for 8-phenylmenthol has appeared in *Organic Syntheses*.¹⁰

Optically pure trans-2-phenylcyclohexanol can also be prepared by resolution of the phthalate esters using brucine to obtain the (+)-alcohol and strychnine to obtain the (-)-alcohol (after basic hydrolysis of their respective salts).¹¹ Enzyme-catalyzed kinetic resolution of the acetate esters using pig liver esterase⁴ and pig liver acetone powder¹² has been used to prepare both enantiomers of this chiral auxiliary. The hydroboration of 1-phenylcyclohexene with isopinocampheylborane has been reported to give the chiral auxiliary in 97% enantiomeric excess.¹³

Racemic trans-2-phenylcyclohexanol has previously been prepared in a yield comparable to that realized in this procedure via copper-catalyzed phenyl Grignard addition to cyclohexene oxide using the more expensive copper(I) oxide.¹⁴

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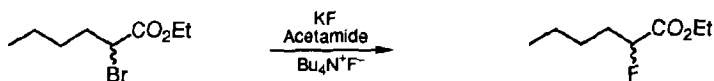
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Appendix

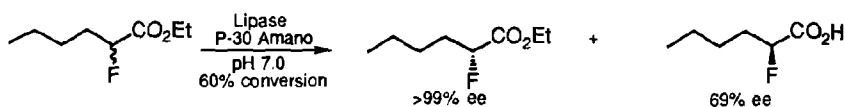
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- (-)-(1R,2S)-trans-2-Phenylcyclohexanol: Cyclohexanol, 2-phenyl-, (1R-trans)- (11); (98919-68-7)
- (+)-(1S,2R)-trans-2-Phenylcyclohexanol: Cyclohexanol, 2-phenyl-, (1S-trans)- (9); (34281-92-0)
- Racemic trans-2-Phenylcyclohexanol: Cyclohexanol, 2-phenyl-, trans-(±)- (9); (40960-69-8)
- Bromobenzene: Benzene, bromo- (8,9); (108-86-1)
- Cyclohexene oxide: 7-Oxabicyclo[4.1.0]heptane (8,9); (286-20-4)
- Chloroacetyl chloride: Acetyl chloride, chloro- (8,9); (79-04-9)
- 4-Dimethylaminopyridine: Pyridine, 4-(dimethylamino)- (8); 4-Pyridinamine, N,N-dimethyl- (9); (1122-58-3)
- Lipase (*Pseudomonas fluorescens*): Lipase, triacylglycerol (9); (9001-62-1)

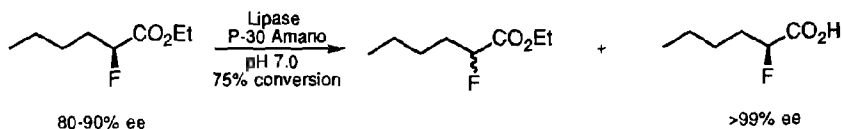
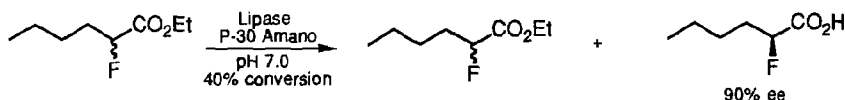
**ENANTIOMERICALLY PURE ETHYL (R)- AND (S)-
2-FLUOROHEXOANOATE BY ENZYME-CATALYZED KINETIC RESOLUTION
(Hexanoic acid, 2-fluoro-, ethyl ester, (R)- and (S)-)**



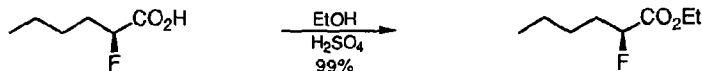
A.



B.



C.



Submitted by P. Kalaritis and R. W. Regenye.¹

Checked by Ronan Guevel and Leo A. Paquette.

1. Procedure

Ethyl 2-fluorohexanoate (Note 1). A 1-L flask equipped with a mechanical stirrer, thermometer, condenser and a gas adapter is charged under an atmosphere of argon with 38.5 g of acetamide and 80 g (0.36 mol) of ethyl 2-bromohexanoate (Note 2). The mixture is heated to 80°C until solution is effected and 38.6 g (0.65 mol) of potassium fluoride (Note 3) is added to it followed by 2.7 mL of tetra-n-butylammonium fluoride (Note 4). The resulting mixture is heated at 140°C with fast stirring for 4-5 hr (Note 5). The reaction mixture is allowed to cool to 90°C and then it is poured into 600 mL of ice. The reaction flask is rinsed with 100 mL of water and 100 mL of dichloromethane, which are added to the ice mixture. The aqueous phase is extracted with dichloromethane (4 x 200 mL). The combined organic layers are dried over anhydrous sodium sulfate and filtered. The dichloromethane solution is then cooled to 5°C and treated under an atmosphere of argon with 15 mL of bromine (Note 6). The reaction is judged complete after ~ 3 hr. It is quenched by adding 200 mL of saturated sodium thiosulfate solution. The two phases are separated and the organic phase is successively partitioned with saturated aqueous sodium bicarbonate solution (2 x 150 mL) and then with 200 mL of brine. It is finally dried over anhydrous sodium sulfate and concentrated to an oil at 40°C/7 mm (Note 7). Vacuum distillation at 36-37°C/0.8-0.9 mm affords 26.2-31.4 g (45-54% yield) of pure ethyl 2-fluorohexanoate as a colorless liquid (Note 8).

Method A. Enantiomerically pure ethyl (R)-2-fluorohexanoate (60% hydrolysis). A 1-L Morton flask equipped with a mechanical stirrer, glass baffle, an electrode connected to a pH control unit and an addition tube connected to a syringe pump, is charged with 300 mL of 0.05 M aqueous phosphate buffer (pH 7.0) (Fisher), 300 mL of deionized water, and 70 g (0.43 mol) of ethyl 2-fluorohexanoate. The resulting mixture is stirred for several minutes and the pH is adjusted to 7.0 with the addition of a few

drops of 0.1 N sodium hydroxide solution. Then 0.43 g of *Pseudomonas* lipase enzyme (P-30, Amano International Enzyme Co., Inc., Troy, Virginia) is added and the hydrolysis is allowed to proceed at 5°C with stirring (reaction time ca. 2 hr). The pH is kept constant at 7.0 by adding 1.0 N sodium hydroxide solution via the syringe pump, which is activated by the pH control unit. The hydrolysis is discontinued when 260 mL of 1.0 N sodium hydroxide solution has been added (60% conversion, Note 9). The mixture is extracted with diethyl ether (5 x 300 mL). The combined organic layers are dried over anhydrous potassium carbonate, filtered, and concentrated at 40°C/70 mm. Vacuum distillation at 36-38°C/0.7-0.8 mm gives 24.0 g (34% yield, 85% of theory, Note 10) of pure ethyl (R)-2-fluorohexanoate, which is 97.5-99% enantiomerically pure, $[\alpha]_D^{25} +13.0$ to $+13.2^\circ$ (CHCl_3 , c 1.3) (Note 9). The aqueous layer is acidified to pH 2 with 3 N hydrochloric acid and extracted with diethyl ether (3 x 500 mL). The combined organic layers are dried over anhydrous sodium sulfate, filtered and concentrated at 40°C/70 mm. The residue is distilled at 71-72°C/0.7 mm to give 30.9 g (53% yield; 89% of theory) of (S)-2-fluorohexanoic acid, which is 53-68% enantiomerically pure (Note 11) $[\alpha]_D^{25} -6.8$ to -8.7° (CHCl_3 , c 1.3).

Method B. Enantiomerically pure ethyl (S)-2-fluorohexanoate. A 1-L, three-necked flask equipped with a mechanical stirrer, glass baffle, an electrode connected to a pH control unit and an addition tube connected to a syringe pump is charged with 300 mL of deionized water, 300 mL of 0.05 M phosphate buffer (pH 7.0) (Fisher), and 80 g (0.49 mol) of racemic ethyl 2-fluorohexanoate. The pH is adjusted to 7.0 with a few drops of 1 N aqueous sodium hydroxide solution, and 23 mg of *Pseudomonas* lipase enzyme (P-30, Amano International) is added to the mixture. The hydrolysis is allowed to proceed at 5-10°C with stirring. The pH is maintained at 7.0 by adding adequate 1 N aqueous sodium hydroxide solution via the syringe pump. The hydrolysis is discontinued when 197 mL (40% conversion) of 1 N aqueous sodium hydroxide solution has been added (total reaction time: 2.5 hr). The reaction mixture

is immediately transferred to an extractor containing 750 mL of ethyl ether. The mixture is agitated for 5 min and the two phases are separated. The aqueous phase is extracted with ethyl ether (3 x 400 mL). The combined organic layers are dried over anhydrous potassium carbonate, filtered and concentrated at 30°C/70 mm to afford 47.2 g (98% of theory) of optically active ethyl (R)-2-fluorohexanoate. The aqueous phase is transferred back into the extractor and carefully acidified to pH 2.0 with concd hydrochloric acid. It is subsequently extracted with diethyl ether (4 x 500 mL). The combined organic layers are dried over anhydrous sodium sulfate and concentrated at 30°C/70 mm to provide 26.1 g (39% yield; 98% of theory) of (S)-2-fluorohexanoic acid (81-86% ee).

Optical purity enhancement: A 1-L, three-necked flask equipped as described above is charged with 28.4 g (0.175 mol) of ethyl (S)-2-fluorohexanoate (81% ee) (Note 12), 300 mL of deionized water and 300 mL of 0.05 M phosphate buffer (pH 7.0). The pH is adjusted to 7.0 with a few drops of 1 N aqueous sodium hydroxide solution and 36 mg of *Pseudomonas* lipase enzyme (P-30, Amano International) is added to the mixture. The hydrolysis is allowed to proceed at 5°C. The pH is kept at 7.0 by adding adequate 1 N aqueous sodium hydroxide solution via the syringe pump. The hydrolysis is discontinued when 131.3 mL (75% conversion) of 1 N aqueous sodium hydroxide solution has been added (total reaction time: 4 hr). The mixture is quickly extracted with ethyl ether (3 x 500 mL). The combined organic layers are dried over anhydrous potassium carbonate and concentrated at 35°C/70 mm to provide 5.66 g of nearly racemic ethyl 2-fluorohexanoate. The aqueous phase is acidified to pH 2.0 with concd hydrochloric acid and extracted with ethyl ether (4 x 500 mL). The combined organic layers are dried over anhydrous sodium sulfate and concentrated at 35°C/70 mm to give 16.8 g (71% yield; 95.5% of theory) of (S)-2-fluorohexanoic acid. This acid is distilled at 67°C/0.4-0.5 mm to give 14.2 g of enantiomerically pure (S)-2-fluorohexanoic acid as a colorless oil: $[\alpha]_D^{25} -13.8^\circ$ (CHCl₃, c 1.7) (Notes 11 and 13).

Method C. Esterification of (S)-2-fluorohexanoic acid. A 250-mL flask is charged with 13.8 g of (S)-2-fluorohexanoic acid, 200 mL of ethanol and 2 mL of concd sulfuric acid. The solution is heated at reflux for 4 hr. Most of the ethanol is distilled slowly at atmospheric pressure and the residue is dissolved in 200 mL of dichloromethane after allowing it to cool to 23°C. The solution is partitioned with 200 mL of saturated aqueous sodium bicarbonate solution and the aqueous layer is back-extracted with 100 mL of dichloromethane. The combined organic layers are washed with 100 mL of brine, dried over anhydrous potassium carbonate and concentrated at 30°C/70 mm to afford 15.6 g (93% yield) of enantiomerically pure (Note 11) ethyl (S)-2-fluorohexanoate as a colorless liquid: $[\alpha]_D^{25} -13.8^\circ$ (CHCl_3 , c 1.0), chemical purity 100% (GC analysis).

2. Notes

1. This procedure was originally used by P. Rosen, G. Holland and R. J. Karasiewicz at Hoffmann-La Roche. A similar procedure has appeared in the literature.²

2. Ethyl 2-bromohexanoate was purchased from Aldrich Chemical Company, Inc.

3. Potassium fluoride was purchased from Fluka and was ground to a fine powder prior to use.

4. Tetra-n-butylammonium fluoride was purchased from Aldrich Chemical Company, Inc.

5. The progress of the reaction was monitored by gas chromatography on an OV-17 column at 100-250°C (20°/min).

6. Bromine was added dropwise keeping the temperature below 10°C at all times. The progress of the reaction was monitored by gas chromatography as

described in Note 4. Bromine was added to brominate the α,β -unsaturated ester that was present as a by-product in the crude material. This procedure simplified the isolation of the ethyl 2-fluorohexanoate by distillation.

7. Some yellow solids appeared upon removing the solvent; they were filtered prior to distillation.

8. The purity of ethyl 2-fluorohexanoate was determined by gas chromatography as described above. The reaction yield varied from 42-70%.

9. % Conversion is based on the amount of base added.

10. % of the theoretical yield is based on the % of conversion.

11. The enantiomeric excess (% ee) of these compounds was determined by the submitters as follows. The ester and acids were first reduced to the corresponding alcohols with DIBAL and LAH, respectively. The alcohols were then allowed to react with 100% excess of (S)-(+)- α -methoxy- α -trifluoromethylphenylacetyl chloride (Mosher's reagent) in (1:1) pyridine-carbon tetrachloride for 18 hr. The diastereomeric ratio of these derivatives was finally determined by isothermal gas chromatography on a capillary OV-17 column at 160°C.

12. This ester was prepared from the optically active (S)-2-fluorohexanoic acid isolated above, by the esterification method described in this procedure.

13. The checkers have noted that the 2-fluorohexanoic acid crystallizes when allowed to stand at room temperature. This material can be recrystallized from pentane at low temperature. The crystals liquify on standing in the open air at room temperature.

3. Discussion

In recent years there has been an increasing interest in the use of enzymes and microorganisms to produce optically active compounds either by means of a kinetic

resolution or by stereospecific chemical transformations (e.g., reductions, oxidations, epoxidations, hydroxylations, etc.).³ Hydrolases in general have been used to effect kinetic resolutions of racemic esters and alcohols via their corresponding esters.⁴ Lipases, a subclass of hydrolases, are commercially available and relatively inexpensive. As a result, they constitute a very attractive class of catalysts for effecting kinetic resolutions, some of which might be difficult by other means.

Lipase P-30 Amano (ex *Psudeomonas fluorescens*) has been found to be synthetically useful in catalyzing very effectively kinetic resolutions of both racemic alcohols and racemic acids via their corresponding esters. This property is not generally observed with other enzymes and, therefore, makes this particular enzyme of greater synthetic utility. The enzyme can tolerate high concentrations of substrates and their hydrolysis products. The rates of the hydrolyses have usually been fast and the enantiomeric excesses achieved high. In most cases, the hydrolyses have been carried out in water and in the absence of co-solvents. These resolutions can be easily accomplished in multi-kilogram scale. A wide variety of substrates have been resolved enantioselectively with this lipase.⁵

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Ethyl (R)-2-fluorohexanoate: Hexanoic acid, 2-fluoro-, ethyl ester, (R)- (12);
(124439-29-8)

Ethyl (S)-2-fluorohexanoate: Hexanoic acid, 2-fluoro-, ethyl ester, (S)- (12);
(124439-31-2)

Ethyl 2-fluorohexanoate: Hexanoic acid, 2-fluoro-, ethyl ester (8,9);

(17841-31-5)

Acetamide (8,9); (60-35-5)

Ethyl 2-bromohexanoate: Hexanoic acid, 2-bromo-, ethyl ester, (±)- (10); (63927-44-6)

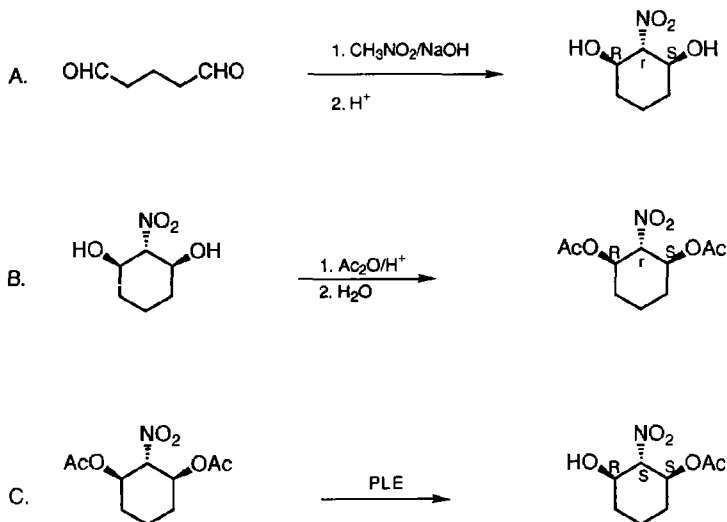
Potassium fluoride (8,9); (7789-23-3)

Tetrabutylammonium fluoride: Ammonium, tetrabutyl-, fluoride (8); 1-Butanaminium,

N,N,N-tributyl-, fluoride (9); (429-41-4)

(S)-2-Fluorohexanoic acid: Hexanoic acid, 2-fluoro-, (S)- (12); (113776-26-4)

**ENANTIOSELECTIVE SAPONIFICATION WITH PIG LIVER ESTERASE
(PLE): (1*S*,2*S*,3*R*)-3-HYDROXY-2-NITROCYCLOHEXYL ACETATE
(1,3-Cyclohexanediol, 2-nitro-, 1-acetate, [1*S*-(1 α ,2 β ,3 α)])**



Submitted by Martin Eberle, Martin Missbach, and Dieter Seebach.¹

Checked by David L. Coffen.

1. Procedure

A. *(1R,2r,3S)-2-Nitrocyclohexane-1,3-diol*. A 1-L, round-bottomed flask, equipped with a magnetic stirrer, a thermometer and an ice/ethanol bath is charged with 175 mL (0.455 mol) of an aqueous 25% solution of glutaric dialdehyde, 38 mL (0.708 mol) of nitromethane and 600 mL of methanol (Note 1). At 0-5°C 12 mL of aqueous 2 M sodium hydroxide is added gradually. The cooling bath is removed and

the reaction mixture is stirred for 4 hr at room temperature. The resulting yellow solution is neutralized by adding 15 g of acidic cation exchange resin and stirring for an additional 20 min (Note 2). The resin is filtered off and washed with a small volume of methanol. The filtrate is evaporated to a semi-solid residue using reduced pressure and a 35°C water bath. The residue is dissolved in 100 mL of absolute ethyl alcohol with heating and diluted by gradual addition of 250 mL of toluene. The resulting two-phase mixture (Note 3) is again evaporated, with azeotropic removal of water. The resulting residue is again taken up in 100 mL of hot ethyl alcohol and diluted with 250 mL of toluene (Note 3). The almost colorless crystals are filtered and dried at high vacuum to yield 44-52 g (60-70%) of nitrodiol, mp 152-155°C (dec.).

B. (1R,2r,3S)-3-Acetoxy-2-nitrocyclohexyl acetate. In a 1-L flask 52 g (0.323 mol) of the nitrodiol are suspended in 150 mL of acetic anhydride. Without cooling, 3-6 drops of concentrated sulfuric acid are added (Note 4). After 1 hr 500 mL of ice/water is rapidly added and stirring is continued for 60 min. The resulting colorless crystals are filtered, washed with water and air dried. The product thus obtained, 75.6 g (95.6%) of colorless crystals, is pure by TLC (4:1 hexane/ethyl acetate) and NMR, and melts at 89-90°C (Note 5).

C. (1S,2S,3R)-3-Hydroxy-2-nitrocyclohexyl acetate. A 500-mL flask equipped with a magnetic stirrer is charged with 10 g (41 mmol) of powdered nitrodiacetate and 300 mL of 0.2 M phosphate buffer of pH 7.0 prepared by dissolving 11 g of potassium dihydrogenphosphate and 3.3 g of potassium hydroxide in 300 mL of deionized (or distilled) water. To the stirred suspension is added 30 mg of purified PLE [Esterase (EC 3.1.1.1), suspended in 2.8 mL of 3.2 M ammonium sulfate buffer] (Note 6) and the mixture is stirred for 24 to 48 hr (Note 7). The continuously-measured pH drops to about 5.6 during the reaction and then remains almost constant, while the mixture has turned to a practically clear, pale yellow solution (Note 8). The solution is filtered through a paper filter and the filtrate is extracted three times with 100 mL of ether. The

organic phase is dried over anhydrous magnesium sulfate and filtered. Removal of the solvent and of the acetic acid under reduced pressure leaves 7-8 g (85-95%) of colorless monoacetate as a crystalline solid (Note 9). Recrystallization by dissolving in 100 mL of ether and adding 250 mL of pentane gives 5-6 g (60-70%) of pure (1S,2S,3R)-3-hydroxy-2-nitrocyclohexyl acetate (Note 10), mp 90-91°C, $[\alpha]_D +9.5^\circ$ (CHCl₃, c 1.0) (Note 11). From the mother liquor, another 1-2 g (12-24%) of monoacetate, mp 89-90°C, can be obtained (Note 12).

2 Notes

1. Commercial grade chemicals were used without further purification. The glutaric dialdehyde solution should be fresh.

2. The checkers used Amberlite IR-120(plus) acid form, capacity 1.9 meg/mL supplied by the Aldrich Chemical Company, Inc.

3. Two layers will form unless the water content of the crude product is sufficiently reduced during the preceding evaporation; in that case, the evaporation is to be repeated.

4. The solution turns clear and the temperature rises to 60-70°C when the reaction has started. More sulfuric acid should be added if a sustained exotherm does not ensue.

5. The submitters recommend recrystallization from alcohol/water (2:1). This is essential if NMR and TLC analyses of the crude nitrodiacetate indicate the presence of monoacetate.

6. The checker used the contents of one 30-mg vial of Sigma material, rinsed in with ca. 1 mL of deionized water. The submitters originally developed the process with PLE purified according to a procedure they had published previously.²

7. The submitters used 45 mg of enzyme and observed the reaction to be complete in 11.5 to 12.5 hr.

8. In addition to the monoacetate, a small amount of diacetate and an even smaller amount of diol could be detected by TLC in the crude product.

9. The crude product is enantiomerically pure according to ^{19}F -NMR of the corresponding Mosher ester (>97% ee). The checker observed lower $[\alpha]_{\text{D}}^{25}$ values (+8.72° and +8.61°) but confirmed the enantiomeric purity by HPLC analysis of the corresponding Mosher esters. By HPLC comparison with the diastereomeric mixture of Mosher esters prepared from a sample of racemic monoacetate (oily substance obtained by partial hydrolysis of diacetate) the (-)-enantiomer content appears to be less than 1%.

10. The absolute configuration of the product has been proved by X-ray analysis of the corresponding camphanic ester.^{2,3}

11. The monoacetate shows the following ^1H NMR spectrum (90 MHz) δ : 1.3-1.9 (m, 4 H), 2.0 (s, 3 H), 2.1-2.2 (m, 2 H), 2.7 (d, $J = 5.5$, OH), 4.1 (m, 1 H), 4.4 (apparent, t, $J = 10.5$, 1 H), 5.1-5.3 (m, 1 H).

12. Recrystallization of this fraction gave another 0.75-1.5 g (10-18%) of pure product.

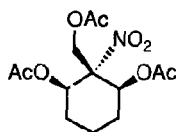
3. Discussion

The use of ester-cleaving enzymes is probably going to be one of the most useful biological-chemical methods in the synthetic laboratory. No example of this type of reaction has hitherto been published in the *Organic Syntheses* series of procedures. So far, the only biological-chemical *Organic Syntheses*-procedures are two yeast reductions,^{4,5} one oxidation with horse-liver-alcohol-dehydrogenase,⁶ and a disaccharide synthesis catalyzed by emulsin.⁷ The procedure described here is

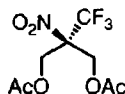
also applicable with crude enzyme powder, but the work-up is a bit more complicated, because a continuous extractor must be used to overcome problems with emulsions. Both crude enzyme concentrate and purified PLE as a mixture of isoenzymes⁸ are commercially available, but the crude concentrate can easily be prepared from fresh pig liver and is thus very cheap.² By using self-made PLE-powder, the submitters have produced amounts of 20-25 g of pure monoacetate per run.²

Several review articles containing discussions of enantioselective syntheses with ester-cleaving enzymes have appeared recently (as of 1987).⁹⁻¹³ Of the many examples, the ones in which meso-substrates are employed are most attractive since the theoretical yield is 100%. In many applications of PLE the enantiomeric excess (% ee) of the product depends crucially upon the source of the enzyme. This effect has not been noticed in the enantioselective saponifications of nitrodiol diacetates, either because the reaction is insensitive to it, or because this complication is overcome by the great crystallization tendency of the products. The only problem we observed when the reaction was carried out with commercial crude PLE-powder (but not with the self made one) was the production of a certain amount of diol which could not be removed by simple recrystallization. In this case, filtration over a short silica gel column with methylene chloride as eluent gives after recrystallization pure monoacetate.

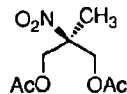
Other examples of enantiomerically pure monoacetates of meso-nitrodiols, which are available using the above procedure, are collected in Table 1. Entries 1 and 3 in Table 1 refer to runs following the above procedure, for all other cases the self made crude PLE-powder was used. Cases in which no reaction (a) or unsatisfactory selectivities (b) were observed, are shown below:



(a)



(a)

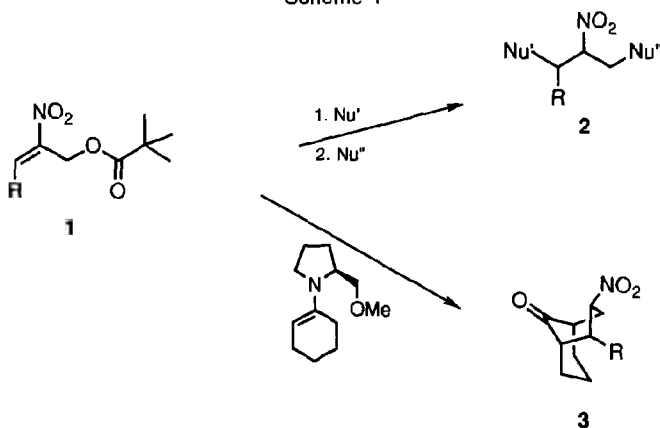


(b)

The meso-nitrodiole starting materials for the preparation of the PLE diacetate substrates are readily obtained from nitromethane or nitroethane and aldehydes or dialdehydes. They crystallize readily. The above procedures for the preparation of nitrocyclohexanediol and its diacetate from glutaraldehyde and nitromethane are modifications of published methods (Lichtenthaler,¹⁴ Baer¹⁵).

The chiral monoacetates now available are useful multiple coupling reagents¹⁶⁻¹⁸ for syntheses of enantiomerically pure target molecules. They can be converted to nitroolefinic allylic esters, achiral or racemic analogues of which we have previously shown¹⁶⁻¹⁸ to combine sequentially with two (different) nucleophiles (see 1-2 in Scheme 1).

Scheme 1



In a first approach to an enantioselective version of this method, we employed¹⁹ chiral enamines derived from proline,²⁰ (see 1-3 in Scheme 1). In this stoichiometric, enantioselective reaction, the valuable auxiliary used has to be recovered (i.e., recycled) in preparative-scale applications.²¹

We then used²² nitroallylic pivalates for the alkylation of hydroxy acid-derived enolates to prepare enantiomerically pure compounds (EPC), (see 4-5 in Scheme 2), an example of the use of the pool of chiral building blocks for EPC syntheses.²³⁻²⁵ Finally, the procedure described here allows for syntheses of EPC with a catalytic enantioselective step²⁶: dehydration of the monoacetate from the PLE saponification leads to (S)-nitrocyclohexenyl acetate **6**, and pivaloylation followed by acetate hydrolysis and dehydration leads to the pivalate **8** of the enantiomeric alcohol. These compounds can be used for substitutions with a variety of nucleophiles.^{2,3,26} Thus, starting from the enantiomerically pure Michael acceptors **6** and **8**, 3-alkyl nitrocyclohexenes **7** and **9**, respectively, of high enantiomeric excess are available (see Scheme 2, Nu = methyl lithium, phenyllithium and the morpholinoenamine of acetophenone):

Scheme 2

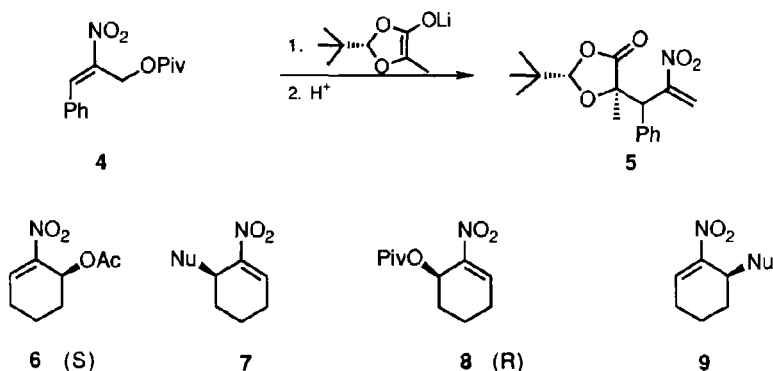
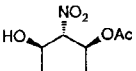
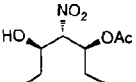
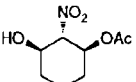
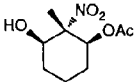
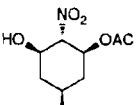
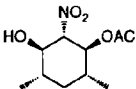
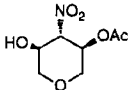
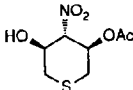
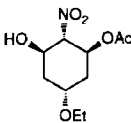


TABLE I

Yields, melting points, and specific rotations of nitrodiol monoacetates which were prepared by procedure C described above by using PLE-powder² instead of purified enzyme. Entries 1 and 3 in Table 1 refer to runs following the above procedure, for all other cases the self made crude PLE-powder was used. The configuration and the sense of chirality of the products of entries 1,3 and 4 were determined by x-ray crystal structure analysis of the camphanic esters, those of the other are inferred by analogy and by NMR comparison. The open chain compounds (entries 1 and 2) were obtained using TES buffer at pH 6.5

Entry No.		Yield [%]	Mp [°C]	$[\alpha]_D$ (CHCl ₃ , c 1)
1		50-70	58-60	-10.5
2		40-50	oil	-10.7
3		60-70	90-91	+ 9.8
4		80-90	106-107	-9.4
5		70-80	91-92	+29.1

6		60-70	130-131	-1.3
7		20-30	111-112	+14.7
8		60-70	130-131 (dec)	+28.1
9		60-70	93-94	+6.0

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(1S,2S,3R)-3-Hydroxy-2-nitrocyclohexyl acetate: 1,3-Cyclohexanediol, 2-nitro-, 1-acetate, [1S-(1 α ,2 β ,3 α)]- (12); (108186-61-4)

(1R,2r,3S)-2-Nitrocyclohexane-1,3-diol: 1,3-Cyclohexanediol, 2-nitro-, (1 α ,2 β ,3 α)- (9); (38150-01-5)

Glutaric dialdehyde: Glutaraldehyde (8); Pentanedial (9); (111-30-8)

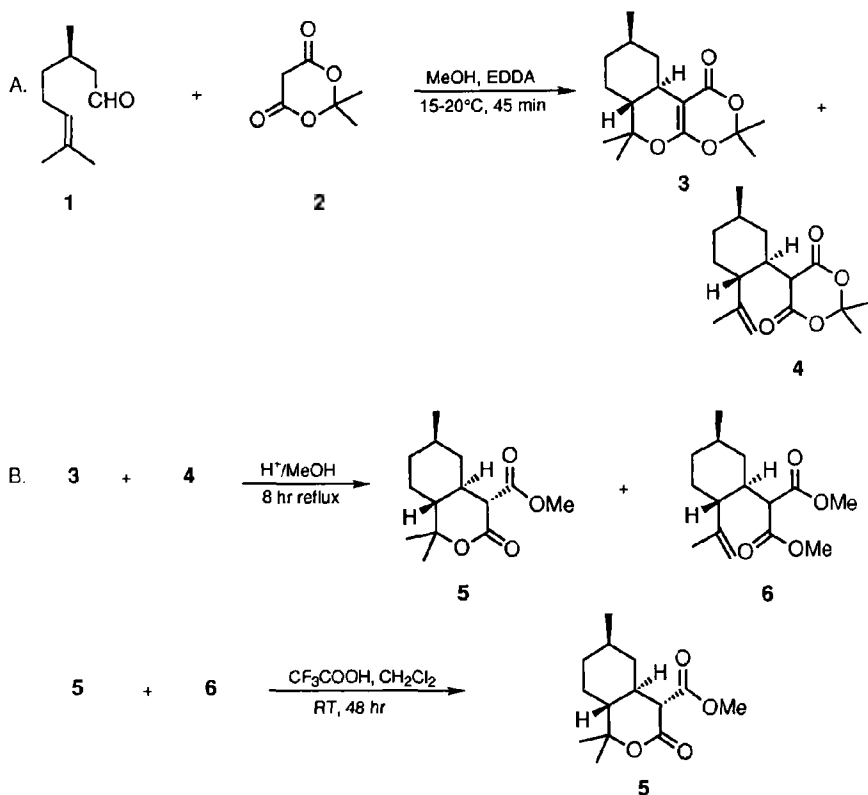
Nitromethane: Methane, nitro- (8,9); (75-52-5)

Amberlite IR-120(plus) acid form: Amberlite IR 120 Plus (10); (78922-04-0)

(1R,2r,3S)-3-Acetoxy-2-nitrocyclohexyl acetate: 1,3-Cyclohexanediol, 2-nitro-, diacetate (ester), (1 α ,2 β ,3 α)- (9); (51269-14-8)

Acetic anhydride (8); Acetic acid anhydride (9); (108-24-7)

**DIASTEREOSELECTIVE FORMATION OF α -METHOXYCARBONYL
LACTONES THROUGH AN INTRAMOLECULAR DIELS-ALDER REACTION:
(4RS,4aRS,6RS,8aRS)-, (4S,4aS,6S,8aS)- AND (4R,4aR,6R,8aR)-
4-METHOXYCARBONYL-1,1,6-TRIMETHYL-1,4,4a,5,6,7,8,8a-
OCTAHYDRO-2,3-BENZOPYRONE [rac-5, (+)-5, and (-)-5]**



Submitted by L. F. Tietze, G. v. Kiedrowski, K.-G. Fahlbusch, and E. Voss.¹

Checked by Charles F. Marth and Edwin Vedejs.

1. Procedure

A. Diels-Alder-adduct rac-3.² A 250-mL round-bottomed flask equipped with a pressure equalizing addition funnel with a calcium sulfate-filled drying tube, a nitrogen inlet, and a magnetic stirring bar is charged with 2,2-dimethyl-1,3-dioxane-4,6-dione **2** (Meldrum's acid) (Note 1, 10.0 g, 69.4 mmol), a catalytic amount of ethylenediammonium diacetate (EDDA) (Note 2, 500 mg, 2.77 mmol) and dry methanol (150 mL). (R,S)-Citronellal (rac-1, Sigma; dried over MgSO₄ and distilled) (Note 3, 9.74 g = 11.4 mL, 63.1 mmol) is added under nitrogen (Note 4) over 15 min through the dropping funnel to the well-stirred mixture while the temperature is kept at 15-20°C by cooling the flask with a water bath. The solution is stirred for an additional 45 min at room temperature, the solvent is removed on a rotary evaporator (25°C), and the remaining yellow oil is dissolved in diethyl ether (300 mL). The organic layer is washed with water (50 mL), saturated sodium bicarbonate (2 x 50 mL), and brine (50 mL), and dried over anhydrous sodium sulfate. Filtration and removal of the solvent gives an 8:1-mixture (16.5 g) of the Diels-Alder adduct rac-3 and the ene-product rac-4 as a yellow oil (Note 5).

B. Lactone 5. The crude mixture of rac-3 and rac-4 is dissolved in 300 mL of dry methanol (distilled from sodium) containing 10 drops of concd hydrochloric acid and heated under reflux for about 8 hr until the reactants can no longer be detected by thin layer chromatography (Note 6). The solvent is removed on a rotary evaporator at 25°C and the remaining residue, which consists of an 8:1 mixture of lactone rac-5 and dimethyl ester rac-6 is dissolved in dry dichloromethane (50 mL). The solution is acidified with trifluoroacetic acid (10 mL) and stirred at room temperature for about 48 hr, until the thin layer chromatogram does not show any dimethyl ester rac-6 (Note 6). The organic layer is washed with water (50 mL), saturated sodium bicarbonate solution (2 x 50 mL), water (50 mL), and brine (50 mL), dried over sodium sulfate,

filtered, and concentrated on a rotary evaporator. Distillation of the remaining thick, yellow oil under reduced pressure in a short path distillation apparatus with an aircooled condenser gives 12.6 g (79%) of rac-5, bp 133-135°C/0.001 mm. The colorless oil is dissolved in tert-butyl methyl ether (10 mL) and hexane (80 mL) and the solvent is allowed to evaporate over 2 days to about 15% of the original volume. Lactone rac-5 (8.11 g, 53%) slowly crystallizes (mp 69-71°C) (Notes 7, 8). If the above procedure is repeated with the mother liquor, a variable additional amount of rac-5 (Note 8) is obtained.

With (S)-citronellal the (4S,4aS,6S,8aS)-lactone (+)-5 is obtained; with (R)-citronellal the (4R,4aR,6R,8aR)-lactone (-)-5 is obtained (Notes 3, 7).

2. Notes

1. Meldrum's acid is commercially available from Merck-Schuchardt, Fluka, or Aldrich Chemical Company, Inc., or it can be prepared by the reaction of malonic acid with acetone.³

2. Ethylenediammonium diacetate (EDDA) is prepared as follows.⁴ A 250-mL, round-bottomed flask with a stirring bar and a pressure equalizing addition funnel with a calcium sulfate-filled drying tube is charged with dry ethylenediamine (12.0 g, 0.20 mol) and dry ether (100 mL). Acetic acid (24.0 g, 0.40 mol) in dry ether (20 mL) is added through the dropping funnel to the stirred solution. The reaction mixture is left at 4°C for 14 hr and the crystals are collected by filtration and washed with ether. Recrystallization from methanol provides 19.8 g (83%) of pure EDDA, mp 114°C, as white needles; IR (KBr) cm^{-1} : 3500-2000 (NH), 2180 (MH_3^+), 1650 (C=O), 1600-1400 (CO_2^-); ^1H NMR (CDCl_3) δ : 1.90 (s, 6 H, CH_3), 3.20 (s, 4 H, CH_2), 5.75 (s, 6 H, NH_3^+).

EDDA is the best catalyst for the condensation. Piperidine acetate gives side products.

3. (R,S)-Citronellal can be purchased from BASF, and (R)-citronellal from Dragoco, Fluka, or Takasago Perfumery Co., Ltd., Japan. (R)-Citronellal can also be synthesized from pulegone with ee >99%.⁵ (S)-Citronellal may be obtained by oxidation of (S)-citronellol,⁶ which is accessible by different routes with ee 95%.⁷ The optical purity of citronellal can be determined by GLC after conversion to the acetal of (-)-(2R,4R)-pentanediol.⁸ For the reactions described, (R,S)-citronellal from BASF, (R)-citronellal from Dragoco, and (S)-citronellol from Fluka were used. (R,S)-Citronellal and (S)-citronellal were distilled under nitrogen before use (bp 83-85°C/11 mm), (S)-citronellal: $[\alpha]_{\text{D}}^{20} -11.5^\circ$ (chloroform, c 0.1); (R)-citronellal ($[\alpha]_{\text{D}}^{20} +13 \pm 1^\circ$) and (S)-citronellol ($[\alpha]_{\text{D}}^{20} -4.9 \pm 0.2^\circ$) were used as purchased.

4. The reaction can also be performed without using inert gas, but the yields may be lower.

5. The pure Diels-Alder adduct **3** can be obtained by crystallization of the crude reaction product from ether/hexane: white needles, mp 104-106°C; IR (KBr) cm^{-1} : 2950, 2930, 2860 (C-H), 1715 (C=O), 1615 (C=C, 1400, 1265; ¹H NMR (CDCl₃) δ : 0.40 (m, 1 H, 4 β -H), 0.7-2.5 (m, 7 H, CH + CH₂), 0.90 (d, 3 H, J = 7, CH₃), 1.23, 1.43, 1.70, 1.73 (s, 3 H, CH₃), 2.75 (dt, 1 H, J₁ = 12, J₂ = 2, 4-H). When the pure Diels-Alder adduct **3** is heated in dry methanol under reflux for 3 hr, **5** (mp 68-70°C) is obtained in 92% yield from **3**.

6. Macherey-Nagel Polygram SIL G/UV254-plates were used with 2:5 v/v ether/hexane as eluant. The Diels-Alder product **3** (R_f = 0.29), is visible under short wavelength ultraviolet light, whereas the detection of **4** (R_f = 0.33), rac-**5** (R_f = 0.22) and **6** (R_f = 0.47) is effected by development in an iodine chamber.

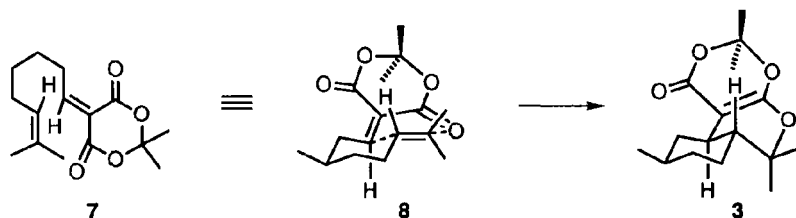
7. The physical properties of rac-**5**, (+)-**5**, and (-)-**5** are as follows: (+)-**5**, $[\alpha]_{\text{D}}^{20} +44.1^\circ$ (chloroform, c 1.004); (-)-**5**, $[\alpha]_{\text{D}}^{20} -44.0^\circ$, (chloroform, c 0.995); IR (KBr) cm^{-1} : 2980, 2950, 2930, 2870, (CH), 1745, 1725 (C=O), 1450, 1320; ¹H NMR (200 MHz, CDCl₃) δ : 0.74 (ddd, 1 H, J = 12, 12, 12, 5 β -H), 0.86-1.7 (m, 5 H, 6, 7 β , 8 α , 8 β -H),

0.95 (d, 3 H, $J = 6.5$, 6-CH₃), 1.36 (s, 3 H, 1 α -CH₃), 1.7-1.9 (m, 2 H, 5 α , 7 α -H), 1.42 (s, 3 H, 1 β -CH₃), 2.16 (dddd, 1 H, $J = 3.5, 12, 12, 12$, 4 α -H), 3.09 (d, 1 H, $J = 12$, 4-H), 3.81 (s, 3 H, OCH₃); ¹³C NMR (50.3 MHz, CDCl₃) δ : 22.0 (1 α -CH₃), 23.3 (6-CH₃), 27.2 (C-7), 28.2 (1 β -CH₃), 31.6, (C-6), 34.2 (C-8), 36.0 (C-8 α), 40.5 (C-5), 45.9 (C-4 α), 52.6 (OCH₃), 55.1 (C-4), 86.6 (C-1), 167.1 (C=O), 169.6 (C-3); MS (70 eV): $m/e = 254$ (1%, M⁺), 239 (6%, M-CH₃), 223 (2%, M-OCH₃), 196 (50%, M-C₃H₆O), 168 (15%, 196-CO), 109 (22%, 168-CO₂CH₃), 101 (100%), 59 (55%, CO₂CH₃).

8. Crystallization of the crude material without distillation from tert-butyl methyl ether/hexane affords 56% of rac-**5**, mp 68-70°C, as pale yellow crystals. The submitters obtained a second crop of 1.5 g from crystallization of distilled material; mp 68-78°C, starting from citronellal purchased from BASF. The checkers found that citronellal from Sigma required distillation and gave an impure second crop of **5** only with difficulty.

3. Discussion

Lactone **5** can be obtained in both enantiomeric forms or as a racemate according to the described procedure. The reaction sequence includes the in situ formation of an alkylidene-1,3-dicarbonyl system **7** which can act as a heterodiene in an intramolecular hetero-Diels-Alder addition. A small amount of the ene product **4** with de > 98% is formed at room temperature as well. The remarkable selectivity in formation of diastereomer **3** is explained by an energetically more favorable exo transition state **8** with a pseudo-chair arrangement having the methyl group quasi-equatorial. Polycyclic cis-fused compounds can also be synthesized by the procedure above,⁹ and a related sequence to the cannabinoid skeleton has been described using appropriate 1,3-dicarbonyl reactants.¹⁰



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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2,2-Dimethyl-1,3-Dioxane-4,6-dione (Meldrum's Acid): Malonic acid, cyclic isopropylidene ester (8); 1,3-Dioxane-4,6-dione, 2,2-dimethyl- (9); (2033-24-1)

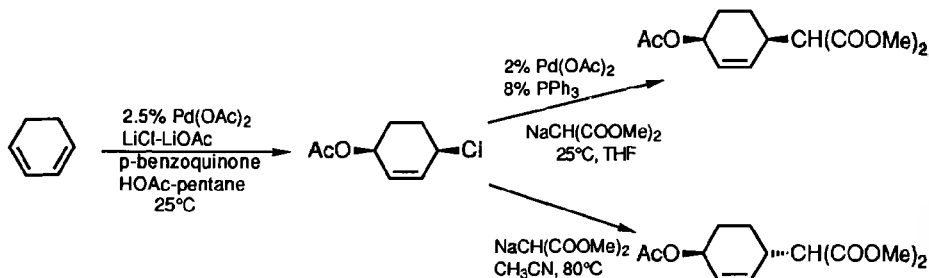
Ethylenediammonium diacetate: 1,2-Ethanediamine diacetate (9); (38734-69-9)

(R)-Citronellal: 6-Octenal, 3,7-dimethyl-, (R)-(+)- (8,9); (2385-77-5)

[6aR-(6a α ,9 α ,10a β)]-Octahydro-3,3,6,6,9-pentamethyl-1H,6H-[1,3]dioxino-[4,5-*c'*][2]benzopyran-1-one: 1H,6H-[1,3]Dioxino[4,5-*c'*][2]benzopyran-1-one, octahydro-3,3,6,6,9-pentamethyl-, [6aR-(6a α ,9 α ,10a β)]- (10); (78394-10-2)

**STEREOSELECTIVE 1,4-FUNCTIONALIZATIONS OF CONJUGATED
DIENES: *cis*- and *trans*-1-ACETOXY-4-(DICARBOMETHOXYMETHYL)-
2-CYCLOHEXENE**

**(Propanedioic acid, [4-(acetyloxy)-2-cyclohexen-1-yl]-,
dimethyl ester, *cis*- and *trans*-)**



Submitted by Jan-E. Bäckvall and Jan O. Vågberg.¹

Checked by Michael R. Sestrick and Albert I. Meyers.

1. Procedure

A. *cis*-1-Acetoxy-4-chloro-2-cyclohexene. A 1-L, one-necked, round-bottomed flask equipped with a magnetic stirring bar is charged with 200 mL of acetic acid, 5.1 g (0.12 mol) of lithium chloride, 12.2 g (0.12 mol) of lithium acetate dihydrate, 0.67 g (3 mmol) of palladium acetate, and 12.9 g (0.12 mol) of p-benzoquinone. The contents of the flask are stirred at room temperature until all components are dissolved, and 300 mL of pentane is added. To the pentane phase of the biphasic system formed is added 4.82 g (60 mmol) of 1,3-cyclohexadiene (Note 1). The reaction mixture is stirred at a moderate rate (Note 2) at room temperature and after 4 hr, 2.87 g (33 mmol) of manganese dioxide (Note 3) is added. After the flask is stirred for another 4

hr at room temperature, the organic phase is separated and saved, and 2.87 g (33 mmol) of manganese dioxide and 20 mL of acetic acid are added to the remaining acetic acid, which is vigorously stirred for 30 min. To the mixture are added 2.6 g (60 mmol) of lithium chloride and 300 mL of pentane. A new portion of 4.82 g (60 mmol) of 1,3-cyclohexadiene is added and the reaction mixture is stirred at a moderate rate (Note 1) at room temperature overnight (12-15 hr). To the reaction mixture is added 70 mL of saturated sodium chloride solution and the organic phase is separated and saved. The aqueous phase is filtered and extracted with pentane (2 x 300 mL). The combined organic phases are washed with water (2 x 120 mL), 120 mL of saturated aqueous sodium carbonate, 120 mL of 2 M sodium hydroxide, 120 mL of water and 120 mL of saturated sodium chloride solution. The organic phase is dried over magnesium sulfate and the solvent is removed by rotary evaporation at reduced pressure giving 16.5-17.5 g (79-84%) of a yellow oil. Kugelrohr distillation (95-105°C, 1 mm) of the crude product affords 14.6-15.6 g (71-75%) of pure *cis*-1-acetoxy-4-chloro-2-cyclohexene (> 98% *cis*). Analysis by HPLC and GLC shows about 1% contamination of diacetate as the only impurity. No dichloride can be detected (< 0.5%).

B. cis-1-Acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene. A 2-L, two-necked, round-bottomed flask equipped with a magnetic stirrer, nitrogen-vacuum inlet, and a rubber septum, is charged with 17.5 g (0.1 mol) of *cis*-1-acetoxy-4-chloro-2-cyclohexene, 0.49 g (2.2 mol) of palladium acetate and 2.4 g (9.0 mmol) of triphenylphosphine (Note 4). The flask is flushed with nitrogen (Note 5). To the flask is added 550 mL of a 0.2 M solution (0.11 mol) of sodium dimethyl malonate in tetrahydrofuran (THF) by syringe (Note 6). The flask is again flushed with nitrogen and the reaction mixture, which now has turned yellow, is stirred at room temperature for 2 hr (Note 7). The flask is opened and 200 mL of saturated aqueous sodium bicarbonate is added. The stirring is continued for 20 min, and then 100 mL of water

and 200 mL of ether are added. The contents of the flask are transferred into a 2-L separatory funnel and the organic phase is separated. The remaining aqueous phase is extracted with ether (3 x 300 mL). The combined organic phases are washed with 200 mL of saturated brine, dried over anhydrous magnesium sulfate, concentrated on a rotary evaporator to approximately 400 mL, and then filtered through a short silica gel column (Note 8). Removal of the rest of the solvent by rotary evaporation at reduced pressure gives 30.4-31.3 g of a light brown oil. Excess dimethyl malonate is removed by Kugelrohr distillation at 100°C (1 mm). Kugelrohr distillation (140°C, 0.2 mm) of the remaining crude product affords 25.9-26.7 g (91%) of cis-1-acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene as a light brown oil. Analysis by GLC indicates a chemical purity of 95-98%.

C. *trans*-1-Acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene. In a 1-L, two-necked flask equipped with a reflux condenser, nitrogen gas inlet, and a magnetic stirring bar are placed 8.73 g (50 mmol) of cis-1-acetoxy-4-chloro-2-cyclohexene and 400 mL of a 0.18 M solution (72 mmol) of sodium dimethyl malonate in acetonitrile (Note 9). The flask is flushed with nitrogen and then heated in an oil bath at reflux for 21 hr. The reaction mixture is cooled to room temperature and 5 g of solid sodium hydrogen carbonate is added. The mixture is stirred for 2 hr, poured into 800 mL of ether and the resulting mixture is filtered. The organic phase is collected and the solvent is removed on a rotary evaporator to afford 16.1 g of the product together with dimethyl malonate. The excess dimethyl malonate is removed by Kugelrohr distillation at 70°C (0.2 mm). The residual crude yellow oil was dissolved in a minimal amount of ethyl acetate and passed through a short silica plug (30-35 g, Alfa 53 micron silica), eluting with a small amount of fresh ethyl acetate. Removal of ethyl acetate on a rotary evaporator and further concentration at 0.2 mm overnight yielded 11.6-12.2 g (86-90%) of *trans*-1-acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene as a clear oil, essentially pure (99% by GLC) (Note 10).

2. Notes

1. 1,3-Cyclohexadiene was obtained from Aldrich Chemical Company, Inc. and distilled before use. It can also be synthesized according to *Org. Synth., Coll. Vol. V* 1973, 285.
2. A stirring rate of 5-10 rps was used (only a small vortex was present).
3. Commercial, active manganese dioxide from Merck-Schuchardt was used.
4. Palladium acetate and triphenylphosphine generate the active tri- or tetrakis(triphenylphosphine)palladium(0) catalyst on addition of sodium dimethyl malonate.
5. A manifold system connected to a vacuum line and a nitrogen line was used.
6. Sodium dimethyl malonate was prepared from equimolar amounts of sodium hydride and dimethyl malonate.
7. The reaction is usually over after 30 min. The reaction was checked by GLC or TLC to confirm completion.
8. This filtration was done in order to remove remaining palladium species and phosphine oxide. A column (4 x 8 cm) packed with Alfa Silica Gel (58 microns) was used.
9. Acetonitrile was stirred overnight with calcium hydride and then distilled onto freshly activated 4 Å molecular sieves.
10. All GLC analyses were performed on a 2.4-m x 6-mm glass column packed with 5% SE-30 on Chromosorb W or crosslinked 50% phenylmethylsilicone.

3. Discussion

This procedure for stereoselective 1,4-functionalization of 1,3-dienes is based on 1,4-acetoxychlorination,² and allows the preparation of 1,4-disubstituted 2-cyclohexenes with full stereocontrol of the carbon-carbon bond formation in the 4-position. It is also highly regioselective. Other procedures^{3,4} for obtaining 4-alkyl-substituted 3-cyclohexenol derivatives use 1,3-cyclohexadiene monoepoxide as starting material. None of the previous methods allow the selective preparation of both stereoisomers as shown here.

The present procedure uses palladium catalysis in the first step and in one of the second steps. These reactions occur under very mild conditions (room temperature) and the catalyst used is commercial palladium acetate.

Since the title compounds can be stereoselectively functionalized in the 1-position by metal-catalyzed nucleophilic substitutions of the acetoxy group, a great number of 1,4-disubstituted 2-cyclohexenes with defined 1,4-relative stereochemistry are available.

While the process works for a great number of conjugated dienes, a few, such as 1,3-cyclopentadiene and those acyclic dienes that have an oxygen substituent in an allylic position, did not give a chloroacetoxylation product.^{2a} Control of the 1,4-relative stereochemistry and preparation of compounds analogous to the title compounds also work for acyclic dienes,^{2a,5} This process was used to obtain remote stereocontrol in acyclic systems and applied to the synthesis of a pheromone.⁵

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

cis-1-Acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene: Propanedioic acid, [4-(acetyloxy)-2-cyclohexen-1-yl]-, dimethyl ester, cis- (11); (82736-52-5)

trans-1-Acetoxy-4-(dicarbomethoxymethyl)-2-cyclohexene: Propanedioic acid, [4-(acetyloxy)-2-cyclohexen-1-yl]-, dimethyl ester, trans- (11); (82736-53-6)

cis-1-Acetoxy-4-chloro-2-cyclohexene: 2-Cyclohexen-1-ol, 4-chloro-, acetate, cis- (11); (82736-39-8)

Lithium acetate dihydrate: Acetic acid, lithium salt, dihydrate (8,9); (6108-17-4)

Palladium acetate: Acetic acid, palladium(2+) salt (8,0); (3375-31-3)

p-Benzoquinone (8); 2,5-Cyclohexadiene-1,4-dione (9); (106-51-4)

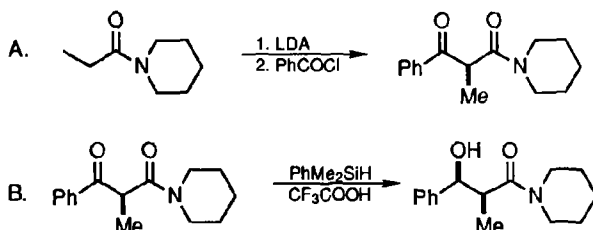
1,3-Cyclohexadiene (8,9); (592-57-4)

Manganese dioxide: Manganese oxide (8,9); (1313-13-9)

Triphenylphosphine: Phosphine, triphenyl- (8,9); (603-35-0)

Dimethyl malonate: Malonic acid, dimethyl ester (8); Propanedioic acid, dimethyl ester (9); (108-59-8)

ERYTHRO-DIRECTED REDUCTION OF A β -KETO AMIDE: ERYTHRO-1-(3-HYDROXY-2-METHYL-3-PHENYLPROPANOYL)PIPERIDINE
(Piperidine, 1-(3-hydroxy-2-methyl-1-oxo-3-phenylpropyl)-, (R^*,R^*)-($\pm$)-)



Submitted by M. Fujita and T. Hiyama.¹

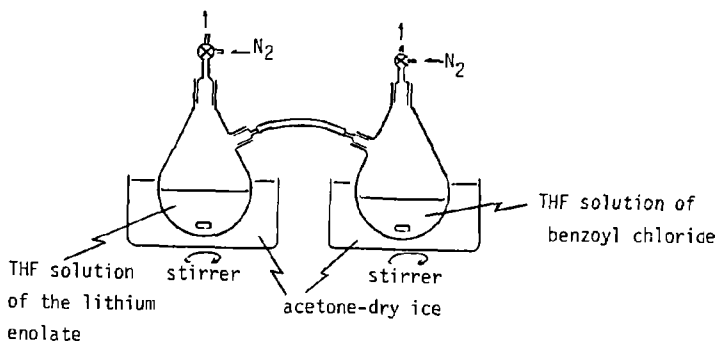
Checked by Gregory P. Roth and Albert I. Meyers.

1. Procedure

A. *1-(2-Benzoylpropanoyl)piperidine*. A dry, 300-mL, two-necked, round-bottomed flask is equipped with a magnetic stirrer and charged with nitrogen. One neck is connected to a three-way stopcock equipped with a balloon filled with nitrogen, and the other neck is capped with a rubber septum. The flask is charged with 100 mL of anhydrous tetrahydrofuran (THF) (Note 1) and 10.1 g (14.1 mL, 0.100 mol) of diisopropylamine (Note 2) and immersed in an acetone-dry ice bath. A 1.68-M hexane solution of butyllithium (60 mL, 0.10 mol) (Note 3) is added dropwise with stirring over a 10-min period, and the stirring is continued for 1 hr at -78°C . To the resulting lithium diisopropylamide (LDA) solution is added dropwise 14.1 g (0.100 mol) of propanoylpiperidine (Note 4) with stirring over a 10-min period, and the stirring is continued for 2 hr at -78°C (Note 5). The rubber septum is replaced with a polyvinyl chloride (or Teflon) tube connected to another 300-mL, two-necked, round-bottomed

flask, which is equipped with a magnetic stirrer and a three-way stopcock, charged with 100 mL of anhydrous THF and 13.5 g (16.3 mL, 0.110 mol) of benzoyl chloride (Note 6), and immersed in an acetone-dry ice bath. The balloon is taken off and nitrogen is passed through the two stopcocks so that the reaction mixture does not come in contact with air (see the apparatus shown in Figure 1). By inclining the first flask, the THF solution of the lithium enolate of 1-propanoylpiperidine is added to the THF solution of benzoyl chloride in the second flask through the polyvinyl chloride tube over a 5-min period. After the solution is stirred for 0.5 hr at -78°C , it is allowed to warm to room temperature, diluted with 200 mL of dichloromethane, and washed with 200 mL of water. The organic layer is separated, and the aqueous layer is extracted with two 50-mL portions of diethyl ether. The combined organic layers are dried over anhydrous magnesium sulfate and concentrated with a rotary evaporator. Recrystallization from diethyl ether-hexane affords 12.5 g (51%) of 1-(2-benzoylpropanoyl)piperidine, mp $100-101^{\circ}\text{C}$ (Note 7).

Figure 1



B. erythro-1-(3-Hydroxy-2-methyl-3-phenylpropanoyl)piperidine. A 300-mL, two-necked, round-bottomed flask is equipped with a magnetic stirrer and charged with nitrogen. One neck is connected with a balloon charged with nitrogen, and the other neck is capped with a rubber septum. Into the flask are placed 50 mL of trifluoroacetic acid (Note 8) and 11.9 g of 1-(2-benzoylpropanoyl)piperidine (48.7 mmol) prepared in Part A; then the flask is immersed in an ice-water bath. To the flask is added 7.3 g of dimethylphenylsilane (8.24 mL, 54 mmol) (Note 9) over a period of 5 min with the aid of a 10-mL syringe, and the resulting mixture is stirred for 4 hr in the ice bath. The mixture is diluted with 200 mL of dichloromethane and washed with 200 mL of water. After the organic layer is separated, the aqueous layer is extracted with two 50-mL portions of diethyl ether, and the combined organic layers are concentrated with a rotary evaporator (Note 10). The crude oil is placed in a 200-mL, one-necked flask and dissolved in 100 mL of methanolic 1 M sodium hydroxide. The solution is stirred for 1.5 hr at ambient temperature with a magnetic stirrer. The mixture is diluted with 200 mL of dichloromethane and washed with 50 mL of water. The organic layer is separated, and the aqueous layer is extracted with two 50-mL portions of diethyl ether. The combined organic layers are dried over anhydrous magnesium sulfate and concentrated by rotary evaporation (Note 11). The residual oil is subjected to column chromatography using 100 g of silica gel (Note 12). After the first fraction (800 mL) of hexane is eluted, the second fraction, eluted with 500 mL of diethyl ether, is collected and concentrated. Recrystallization of the resulting oil from diethyl ether-hexane gives 10.2 g of material, mp 85-86°C. The yield is 90% (Note 13).

The analogous threo derivatives can be made by use of tris(diethylamino)sulfonium difluorotrimethylsilicate as the catalyst (Note 14).

2. Notes

1. Tetrahydrofuran (THF) is freshly distilled over benzophenone ketyl.
2. Diisopropylamine is distilled over calcium hydride.
3. The hexane solution of butyllithium is purchased from Wako Pure Chemicals Industries, LTD, and titrated before use.
4. Propanoylpiperidine is prepared from propanoyl chloride and piperidine according to a similar procedure described in ref. 2.
5. The lithium enolate of (2-benzoylpropanoyl)piperidine should be handled below -20°C , as it decomposes above 0°C .
6. Benzoyl chloride of commercial grade is distilled before use.
7. Spectral characteristics are as follows: ^1H NMR (CDCl_3) δ : 1.46 (d, 3 H, $J = 7.2$), 1.3-1.7 (m, 6 H), 3.25-3.65 (m, 4 H), 4.40 (q, 1 H, $J = 7.2$), 7.25-7.65 (m, 3 H), 7.85-8.05 (m, 2 H); IR (KBr) cm^{-1} : 1696, 1620, 1450, 1204, 686; MS (50 eV) m/z rel intensity) 245 (M^+ ; 14), 140 (37), 105 (100), 84 (99), 77 (47). Anal. Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.22; H, 7.87; N, 5.69.
8. Trifluoroacetic acid was purchased from Aldrich Chemical Company, Inc. (also available from Tokyo Kasei Co. LTD, Japan), and used directly.
9. Dimethylphenylsilane was purchased from Aldrich Chemical Company, Inc. (also available from Shin-etsu Kagaku Co. LTD, Japan), and used directly.
10. About half of the product is trifluoroacetylated during the concentration procedure.
11. A 400-MHz ^1H NMR analysis of the crude oil showed exclusive formation of the erythro isomer of the material (>99:1).
12. A glass column (35 mm x 20 cm) packed with Wakogel C-200 is used.
13. Spectral characteristics are as follows: ^1H NMR (CDCl_3) δ : 1.03 (d, 3 H, $J = 7$), 1.3-1.7 (m, 6 H), 2.84 (dq, 1 H, $J = 2.5, 3$), 3.2-3.7 (m, 4 H), 4.30 (broad s, 1 H), 5.06

(d, 1 H, J = 2.5), 7.2-7.4 (m, 5 H); IR (KBr) cm^{-1} : 3350, 1606; MS (rel intensity) m/z, 247 (M^+ ; 7), 232 (20), 141 (100), 112 (26), 84 (43), 79 (20). Anal. Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_2$ C, 72.84; H, 8.56; N, 5.66. Found: C, 72.74; H, 8.69; N, 5.52.

14. *threo*-1-(3-Hydroxy-2-methyl-3-phenylpropanoyl)piperidine. A 300-mL, two-necked, round-bottomed flask is equipped with a magnetic stirrer and charged with dry nitrogen. One neck is connected with a three-way stopcock, one arm of which is connected to a balloon filled with nitrogen. The other neck is capped with a rubber septum. The flask is evacuated with a vacuum pump under heating with a heat-gun and nitrogen is admitted. This operation is repeated three times to replace the inner atmosphere of the flask completely with dry nitrogen. In the flask are placed 50 mL of hexamethylphosphoric triamide (Note 15), 12.3 g of 1-(2-benzoylpropanoyl)piperidine (50 mmol), and 8.2 g of dimethylphenylsilane (9.2 mL, 60 mmol) by syringe, and then the flask is immersed in an ice-water bath. To the flask is added dropwise 2.5 mL of a 1 M tetrahydrofuran (THF) solution of tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF) (2.5 mmol) (Note 16) with the aid of a syringe, and the resulting mixture is stirred for 6 hr at ice-bath temperature. In order to complete the reaction, 3.4 g of dimethylphenylsilane (3.8 mL, 25 mmol) and 1.5 mL of a 1-M THF solution of TASF (1.5 mmol) are added and stirring is continued for an additional 6 hr at the same temperature. The mixture is quenched with 50 mL of 1 M hydrochloric acid, stirred for 1.5 hr at ambient temperature, and extracted with three 100-mL portions of diethyl ether. The organic layer is washed with 50 mL of water, dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator. The crude oil is subjected to column chromatography using 100 g of silica gel (Note 17). After the first fraction, eluted with 800 mL of hexane, is removed, the second fraction, eluted with 500 mL of diethyl ether, is concentrated (Note 18). Recrystallization of the residue from diethyl ether-hexane gives 8.03 g (65%) of material, mp 79-80°C (Note 19). The mother liquor is concentrated and again subjected to column chromatography (Note

20) to give the same material, which, after recrystallization from diethyl ether-hexane, melts at 77-79°C (1.5 g, 12%). The total yield amounts to 77%.

15. Hexamethylphosphoric triamide is distilled from calcium hydride under reduced pressure of nitrogen. In place of hexamethylphosphoric triamide, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone (DMPU), which is dried and purified similarly,⁷ can be used.

16. TASF was prepared according to the procedure of reference 3. Typically, diethylamino(trimethyl)silane (6.4 g, 8.3 mL, 44 mmol) is added drop by drop under a dry inert atmosphere to an ethereal solution (20 mL) of diethylaminosulfur trifluoride (DAST, purchased from Aldrich Chemical Company, Inc., and used directly) (3.2 g, 2.4 mL, 20 mmol) under cooling with a dry ice/acetone bath. The mixture is allowed to warm to room temperature and stirred for 72 hr at room temperature. The initial homogeneous solution separates into two layers. The upper layer is removed with the aid of a syringe. The lower layer is washed with dry ether (10 mL x 3) and dried under reduced pressure to afford TASF as a solid (6.0 g, 16.6 mmol, 83% yield). All the isolation operations should be carried out under an inert atmosphere such as nitrogen. The solid is dissolved in THF to give a 1-M solution (the volume of the solution is 16.6 mL) which is stored under a dry nitrogen atmosphere.

17. A glass column (35 mm x 20 cm) packed with Wakogel C-200 is used.

18. A 400-MHz ¹H NMR analysis of the crude oil showed exclusive formation of the threo isomer of the material (>99%).

19. Spectral characteristics are as follows: ¹H NMR (CDCl₃) δ: 1.22 (d, J = 7.3 H), 1.1-1.7 (m, 6 H), 2.8-3.8 (m, 5 H), 4.7-4.8 (m, 2 H), 7.31 (s, 5 H); IR (KBr) cm⁻¹: 3380, 1606; MS (rel intensity) m/z 247 (M⁺; 6), 232 (16), 141 (100), 112 (23), 84 (39), 79 (15). Anal. Calcd for C₁₅H₂₁NO₂: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.70; H, 8.63; N, 5.65.

20. A glass column (20 mm x 25 cm) packed with 50 g of Wakogel C-200 is used. After the first fraction, eluted with 300 mL of dichloromethane, was removed, the second fraction, eluted with 300 mL of dichloromethane-diethyl ether (1:4), was concentrated.

3. Discussion

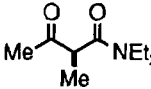
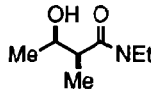
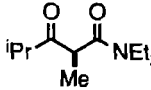
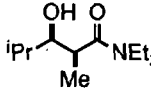
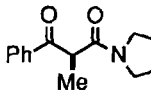
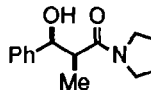
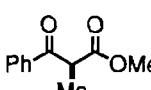
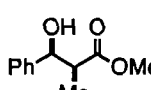
Aldols of the erythro configuration are prepared by aldol condensation of various metal enolates.⁴ An alternative approach is reduction of β -keto esters⁵ or amides⁶ with zinc borohydride. The hydrosilane-based reduction described here provides erythro aldols under high stereocontrol and is practical because of the mild conditions and easy handling of readily available hydrosilanes.⁷ The scope of this reduction is summarized in Table I. No epimerization at the chiral center is observed as shown in the last entry. The erythro-selective reduction with the $\text{PhMe}_2\text{SiH}/\text{CF}_3\text{COOH}$ reagent is also applicable to the reduction of 2-oxy or 2-amino ketones.^{8,9}

Preparation of threo aldols is sometimes a problem. For stereoselective synthesis by aldol condensation, propionate esters of mesitol must be employed.¹⁰ A general, alternative approach to threo aldols is threo-directed reduction of β -keto esters.¹¹ Although the stereoselectivity of this reduction is usually low, reduction of β -keto amides with potassium triethylborohydride (KBHET_3) is extremely selective.¹² The hydrosilane/ F^- reduction of β -keto amides provides threo aldols of high diastereomeric purity when aryl-substituted amides are employed.⁷ The scope of this reduction is summarized in Table II. High threo selectivity is observed only for reduction of 2-arylpropanoates, whereas the reduction of 2-alkanoylpropanoates proceeds with poor selectivity and gives erythro isomers as the major product.¹³ The

hydrosilane/F⁻ reduction is also applicable to the threo-selective reduction of α -oxy and α -amino ketones.⁶

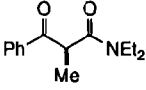
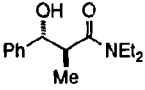
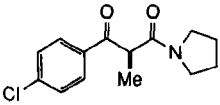
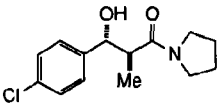
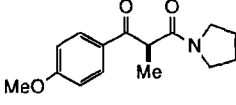
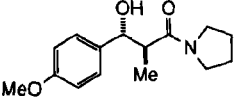
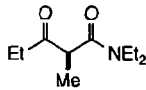
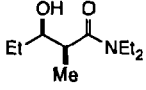
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TABLE I
ERYTHRO-SELECTIVE REDUCTION OF α -SUBSTITUTED β -KETO
ACID DERIVATIVES WITH $\text{PhMe}_2\text{SiH}/\text{H}^+$ REAGENTS^a

Substrate ^b	Time, hr	Product ^c	% Yield ^d	Threo: Erythro ^e
	3		94	2 : 98
	20		89	1 : 99
	3		99	1 : 99
	3		87	1 : > 99

^aCarried out on a 0.5-1.0 mmol-scale at 0°C employing PhMe_2SiH (1.2 mol equiv) and CF_3COOH (1-2 mL/mmol). ^bRacemates were employed unless noted. ^cMajor isomers are shown. ^dPurified by silica gel chromatography. ^eThe ratio was determined by 90 or 400 MHz ^1H NMR analysis. ^fThe optically pure substrate was prepared according to a known method: Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154.

TABLE II
THREO-SELECTIVE REDUCTION OF β -KETO AMIDES
WITH $\text{PhMe}_2\text{SiH/F}^-$ REAGENT ^a

Substrate ^b	Time hr	Product ^c	% Yield ^d	Threo : Erythro ^e
	12		98	>99 : 1
	16		86	99 : 1
	16		92	99 : 1
	22		93	23 : 77

^aCarried out on a 0.5-1.0 mmol scale at 0°C employing PhMe_2SiH (1.2 mol equiv) and TASF (10 mol %). ^bRacemates were employed. ^cMajor isomers are shown. ^dPurified by silica gel chromatography. ^eThe ratio was determined by 90 or 400 MHz ^1H NMR analysis.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

erythro-1-(3-Hydroxy-2-methyl-3-phenylpropanoyl)piperidine: Piperidine, 1-(3-hydroxy-2-methyl-1-oxo-3-phenylpropyl)-, (R*,R*)-(±)- (11); (99114-36-0)

1-(2-Benzoylpropanoyl)piperidine: Piperidine, 1-(2-methyl-1,3-dioxo-3-phenylpropyl)-, (±)- (11); (99114-34-8)

Propanoylpiperidine: Piperidine, 1-propionyl- (8); Piperidine, 1-(1-oxopropyl)- (9); (14045-28-4)

Propanoyl chloride: Propionyl chloride (8); Propanoyl chloride (9); (79-03-8)
Piperidine (8,9); (110-89-4)

Benzoyl chloride (8,9); (98-88-4)

Trifluoroacetic acid: Acetic acid, trifluoro- (8,9); (76-05-1)

Dimethylphenylsilane: Silane, dimethylphenyl- (8,9); (766-77-8)β

Tris(diethylamino)sulfonium difluorotrimethylsilicate: Sulfur (1+), tris(N-ethylethanaminato)-, difluorotrimethylsilicate (1-) (10); (59201-86-4)

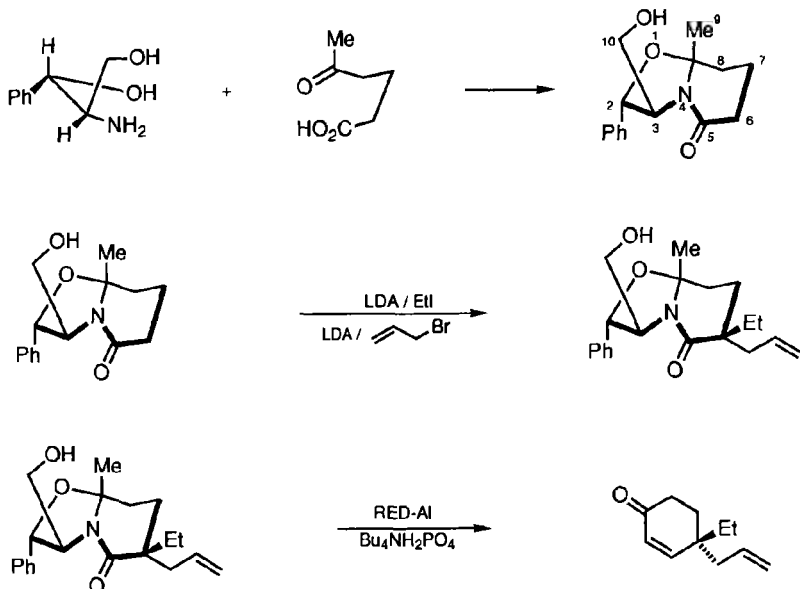
threo-1-(3-Hydroxy-2-methyl-3-phenylpropanoyl)piperidine, (R*,S*)-: Piperidine, 1-(3-hydroxy-2-methyl-1-oxo-3-phenylpropyl)-, (R*,S*)-(±)- (11); (99114-35-9)

1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone: 2(1H)-Pyrimidinone, tetrahydro-1,3-dimethyl- (8,9); (7226-23-5)

Diethylaminotrimethylsilane: Silanamine, N,N-diethyl-1,1,1-trimethyl- (8,9); (996-50-9)

Diethylaminosulfur trifluoride: Sulfur, (diethylaminato)trifluoro- (9); (38078-09-0)

**ASYMMETRIC SYNTHESIS OF 4,4-DIALKYL-CYCLOHEXENONES
FROM CHIRAL BICYCLIC LACTAMS:
(R)-4-ETHYL-4-ALLYL-2-CYCLOHEXEN-1-ONE**



Submitted by Albert I. Meyers and Daniel Berney.¹

Checked by P. B. Madan, A. Schwartz, and David L. Coffen.

1. Procedure

A. *Hexahydro-3-(hydroxymethyl)-8a-methyl-2-phenyl[2S,3S,8aR]-5-oxo-5H-oxazolo[3,2-a]pyridine (Bicyclic lactam).* To a warm solution of (1S,2S)-(+)-2-amino-1-phenyl-1,3-propanediol (32.4 g, 194 mmol) (Note 1) in toluene (800 mL), 5-oxo-

hexanoic acid (25 g, 912 mmol) (Note 2) is added with stirring. The stirred mixture is heated to reflux under argon with azeotropic removal of water for 18 hr. The reaction mixture is cooled, washed with 0.5 N hydrochloric acid (100 mL) and with saturated sodium bicarbonate solution (50 mL), dried over magnesium sulfate, and evaporated to dryness. The residue is crystallized from methylene chloride/hexane in the cold. The crystals are collected by filtration and washed with cold ether to give 35.9-37.2 g (71-74% yield) of the bicyclic lactam in two crops (Note 3).

B. Hexahydro-6-ethyl-3-(hydroxymethyl)-6-allyl-2-phenyl[2S,3S,6S,8aR]-5-oxo-5H-oxazolo[3,2-a]pyridine. In an oven-dried, 500-mL, round-bottomed flask, containing a magnetic stirring bar, is placed 14.4 g (55.2 mmol) of dry bicyclic lactam prepared in Part A. The flask is flushed with argon and filled with 150 mL of anhydrous tetrahydrofuran (Note 4) and then sealed with a rubber septum. The air in the flask is further replaced by argon (Note 5). After dissolution of the bicyclic lactam, the flask is cooled in dry ice/acetone and the solution is stirred while preparing lithium diisopropylamide (LDA).

To an oven-dried, 200-mL, conical flask (Note 6) with air replaced by argon, containing 50 mL of dry tetrahydrofuran (THF) and sealed with a rubber septum, 13.9 g (19.3 mL, 137.4 mmol) of diisopropylamine (Note 7) is added with a syringe. The flask is placed in an ice-water bath. After 15 min, 84 mL (134.4 mmol) of 1.6 M butyllithium in hexane (Note 8) is slowly added with a syringe and with gentle swirling of the flask. The solution is kept for 5 min at this temperature.

The lithium diisopropylamide solution prepared above is transferred dropwise, via a cannula, into the bicyclic lactam solution. The dry ice/acetone bath is replaced by an ice-water bath, where the reaction mixture is kept for 40 min to complete formation of the lithium enolate. The reaction mixture is cooled again (30 min) with a dry ice/acetone bath. Freshly distilled ethyl iodide (25.8 g, 13.4 mL, 165.4 mmol) (Note 9) is added slowly, via syringe, to the mixture and stirring is continued for 55 min in a

dry ice/acetone bath. The cooling bath is replaced by an ice-water bath, the mixture is stirred for exactly 40 min (Note 10), and is poured immediately into a separatory funnel containing 400 mL of 1.0 N hydrochloric acid. The resulting emulsion is extracted once with 400 mL of ether and the organic layer is washed with 200 mL of a 1:1 mixture of brine and a saturated solution of sodium bicarbonate. The ether extract is dried over magnesium sulfate and evaporated to dryness in a 500-mL round-bottomed flask. The residue is dissolved in 60 mL of dry toluene and evaporated again using a water bath (60°C for 45 min) to remove all traces of water and toluene. The product (17.2 g, > 100%) is used in the next step without further purification.

The 500-mL flask containing the crude dry product (17.2 g) is filled with argon and dry tetrahydrofuran (150 mL), a magnetic stirring bar is added, the flask is sealed with a rubber septum, and argon introduced once again. The flask is gently swirled until the viscous oil is totally dissolved and then the flask is immersed in a dry ice/acetone bath.

Another portion of LDA is prepared as described above except that this time 12.6 g of diisopropylamine (17.6 mL, 124.6 mmol) in THF (50 mL) and 78.0 mL (124.8 mmol) of 1.6 M butyllithium/hexane are used. The LDA solution is added, through a cannula, to the ethylated bicyclic lactam solution and the mixture is allowed to warm to 0°C; it is kept at this temperature for 3.0 hr (Note 11). The solution is cooled to -75° - -80°C in a dry ice/acetone bath. A solution of 9.4 g of freshly distilled allyl bromide (6.8 mL, 77.6 mmol) (Note 12) in dry THF (50 mL) is prepared in a 100-mL, oven-dried conical flask flushed with argon and sealed with a rubber septum. This solution is cooled in a dry ice/acetone bath and slowly added to the reaction mixture through a cannula (Note 13). After addition of the allyl bromide, the mixture is kept in a dry ice/acetone bath for 2.5 hr; then the bath is replaced by acetone at -50°C which is allowed to warm to -30°C within a period of 45 min (Note 14). The reaction is terminated by pouring it into 1 N hydrochloric acid (as above), extracting with ether,

washing with sodium bicarbonate-brine, drying over magnesium sulfate, and evaporating the solvents. The viscous or solid residue is dissolved in methylene chloride (10 mL), and petroleum ether (30-60°C) (140 mL) is added. The product is allowed to crystallize at room temperature for 1 hr, then at -15°C overnight, to give 13.5 g (74%, mp 90-92°C) of 9:1 mixture of diastereoisomers.

This mixture is recrystallized three times with the same mixture of solvents and the product is collected after 1 hr at 0°C to give 8.7 g (47.9%, mp 101-103°C) of a 25:1 mixture of diastereoisomers (values based on the 8a-methyl signal integration on NMR spectra) (Note 15).

C. (R)-4-Ethyl-4-allyl-2-cyclohexen-1-one. In an oven-dried, 500-mL, round-bottomed flask, containing dry toluene (300 mL) and a magnetic stirring bar, is placed the dialkylated lactam (7.8 g, 23.7 mmol). The solution is cooled in a dry ice/acetone bath and a 1 M solution of Red-Al in toluene (55 mL, 55.0 mmol) is slowly added (Note 16). The flask is flushed with argon and sealed with a rubber septum which is connected by a hypodermic needle to a rubber balloon filled with argon. The reaction mixture is allowed to warm to room temperature and stirred for 3 days. The septum is removed, the reaction mixture is cooled to 0°C, and methanol (10 mL) is cautiously added with stirring to destroy excess Red-Al. The solution is poured over 1 M aqueous potassium hydroxide (500 mL) in a 2-L separatory funnel and thoroughly shaken with ether (200 mL) until both layers become almost clear. The aqueous layer is extracted twice more with ether (2 x 100 mL) and, after the ethereal layers are combined, the ethereal solution is dried over magnesium sulfate and evaporated to dryness in a 500-mL flask.

The residue is dissolved in ethanol (250 mL), a 1 M aqueous solution of tetrabutylammonium dihydrogen phosphate (80 mL) (Note 17) is added, and the mixture is stirred under reflux for 24 hr. After the solution is cooled, it is partly evaporated on a rotary evaporator with a bath temperature not exceeding 40°C (Note

18) to remove most of the ethanol. Water is added (500 mL) and the solution is extracted twice with chloroform (200 mL). The chloroform extracts are washed with a 1:1 mixture of brine and 1 N hydrochloric acid and then with brine and saturated sodium bicarbonate solutions. Both aqueous phases are extracted twice with chloroform and the extracts are combined, dried over magnesium sulfate, and evaporated to dryness to give 5.8 g of crude 4,4-disubstituted cyclohexenone. The product is distilled rapidly in a Kugelrohr apparatus at 3.5 mm and 115°C to give 3.0 g (77%) of highly pure cyclohexenone (Note 19).

2. Notes

1. The amino diol was purchased from Aldrich Chemical Company, Inc. and was recrystallized before use from methanol/ethyl acetate (the material used had mp 111-113°C).

2. 5-Oxohexanoic acid was purchased from Aldrich Chemical Company, Inc. and was used without further purification.

3. The bicyclic lactam thus prepared has the following physical properties: mp 98-99°C; $[\alpha]_D^{21} + 13.54^\circ$ (EtOH, c 1.55); IR (KBr) cm^{-1} : 3360, 2950, 1625, 1500, 1395; ^1H NMR (270 MHz, CDCl_3) δ : 3.75 (dd, C_{10}H , $J = 11.3, 8.5$), 3.90 (dd, C_{10}H , $J = 11.3, 1.9$), 4.07 (dt, C_3H , $J = 8.5, 1.9$), 4.79 (d, C_2H , $J = 8.6$), 4.89 (br s, 1 H, OH), 7.38 (s, 5 H, phenyl) and unresolved signals.

4. THF was distilled from a blue solution of benzophenone ketyl obtained by refluxing THF in the presence of a sodium dispersion in paraffin and benzophenone.

5. All reactions were done under argon atmosphere. The argon was introduced through hypodermic needles at a pressure below 50 mm across the rubber septum. An exhaust line was also provided to remove air or excess pressure.

6. A conical flask was used in order to allow efficient transfer of the LDA solution.

7. Commercial diisopropylamine was distilled over calcium hydride and stored over potassium hydroxide or 4 Å molecular sieves.

8. 1.6 M Butyllithium in hexane was purchased from Aldrich Chemical Company, Inc.

9. Ethyl iodide was distilled over anhydrous potassium carbonate and stored in the refrigerator over copper turnings.

10. If the reaction mixture is kept for longer than 40 min in the ice water bath, undesirable amounts of the diethylated product are produced.

11. This is the minimum time to allow complete enolate formation.

12. Allyl bromide was distilled over anhydrous potassium carbonate and stored in the refrigerator over 4 Å molecular sieves.

13. The allyl bromide solution was allowed to cool efficiently by dripping it against the cold walls of the flask. It is important that allyl bromide reach the reaction mixture at the lowest possible temperature in order to obtain an optimal stereoselective alkylation. The cannula was protected against heat exchange with air by coating it with a fine rubber tubing.

14. Dry ice was removed leaving only acetone in the Dewar vessel. The temperature was then adjusted to -50°C by adding warm (room temperature) acetone; the temperature was allowed to rise slowly to -30°C by adding small portions of acetone.

15. The physical properties for the dialkylated bicyclic lactam are as follows:
[α]_D²¹ +38.89° (EtOH, c 1.77); IR (KBr) cm⁻¹: 3250, 2490, 1600, 1450, 1370, 1330, 1070, 890, 750; ¹H NMR (270 MHz, CDCl₃) δ : 0.91 (t, 3 H, C₁₂H, J = 7.3), 1.57 (s, 3 H, C₉H); 2.42 (ddd, 2 H, C₁₃H, J = 63.6, 13.4, 7.4), 3.65 (br, 1 H, OH), 3.75 (dd, C₁₀H, J = 11.3, 8.8), 3.90 (dd, C₁₀H, J = 11.2, 2.5), 4.13 (dt, C₃H, J = 8.8, 2.5), 4.78 (d, C₂H, J =

8.5), 5.11-5.16 (m, 2 H, C₁₅H), 5.73-5.88 (m, C₁₄H), 7.37 (s, 5 H, phenyl) and unresolved signals. Anal. Calcd for C₂₀H₂₇NO₃: C, 72.91; H, 8.26; N, 4.25. Found: C, 72.77; H, 8.25; N, 4.24.

16. 1 M Red-Al is prepared by diluting to 100 mL with toluene, 29.5 mL of commercially available 3.4 M Red-Al solution in toluene (Aldrich Chemical Company, Inc.; the checkers used Vitride brand supplied by Hexcel Corp.). Before use, this solution should be warmed to room temperature since it tends to separate into two layers at low temperatures. The first mL of Red-Al produces a vigorous evolution of gas; therefore, the flask should be kept open until the Red-Al addition is complete. Then the reaction vessel is sealed as described.

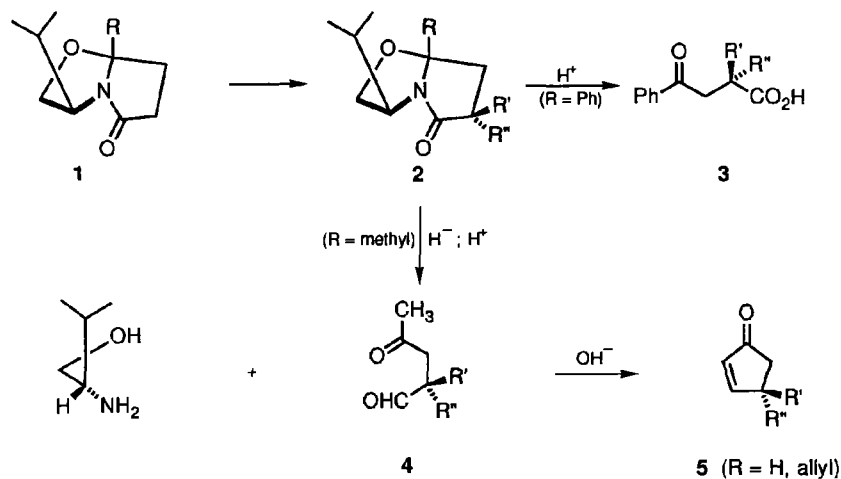
17. 1 M Tetrabutylammonium dihydrogen phosphate aqueous solution was purchased from Aldrich Chemical Company, Inc.

18. The product has a high vapor pressure and can easily be lost by evaporation. Thus, the yields will vary due to this property. The more caution exerted in the evaporation and distillation step, the higher will be the yield of product.

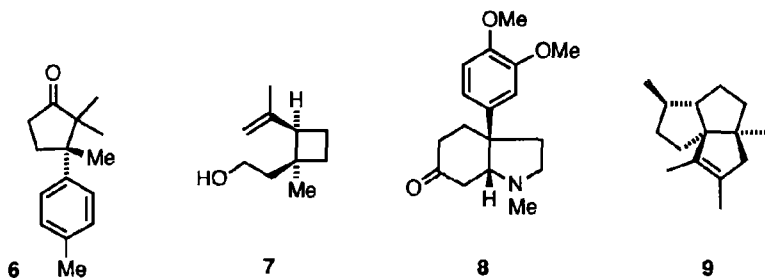
19. If the distillation is performed slowly, a substantial amount of the product may polymerize, resulting in lower yield. The physical data are as follows: $[\alpha]_D^{21}$ -23.12° (EtOH, c, 1.67); IR (film) cm⁻¹: 2960, 1680, 1450, 1380, 1210; ¹H NMR (270 MHz, CDCl₃) δ: 0.95 (t, 3 H, C₈H, J = 7.6), 1.49-1.57 (m, 2 H, C₃H), 1.87 (t, 2 H, C₅H, J = 6.8), 2.23 (d, 2 H, C₉H, J = 6.6), 2.45 (t, 2 H, C₆H, J = 6.8), 5.07-5.14 (m, C₁₁H), 5.65-5.82 (m, C₁₀H), 5.94 (d, C₂H, J = 10.3), 6.71 (d, C₃H, J = 10.3). Anal. Calcd for C₁₁H₁₆O: C, 80.45; H, 9.82. Found: C, 79.67; H, 10.05. By GLC analysis, the product is 93-95% pure with 5-7% of diethylcyclohexenone detectable by GLC-MS.

3. Discussion

Chiral bicyclic lactams such as those described here are useful in reaching a variety of chiral quaternary carbon derivatives. Thus, **1** can be doubly alkylated to the



bicyclic lactam **2** in high diastereoselectivity. Acidic hydrolysis leads to α,α -substituted γ -keto acids **3**,² whereas reduction and hydrolysis furnish the chiral keto aldehydes **4**. Base-catalyzed aldolization affords chiral cyclopentenones **5**.³ In addition, several total syntheses of natural products have been accomplished, further demonstrating the synthetic usefulness of these bicyclic lactams **1**. Thus, (-)- α -cuparenone (**6**),⁴ (-)-grandisol (**7**),⁵ (+)-mesembrine (**8**),⁶ and (-)-silphiperfol-6-ene (**9**)⁷ have been prepared in high enantiomeric excess.



To reach chiral cyclohexenones, we have found that the bicyclic lactam **10**, derived from 5-oxohexanoic acid and the commercially available amino diol, gave excellent results. A number of examples were obtained (Table I).⁸

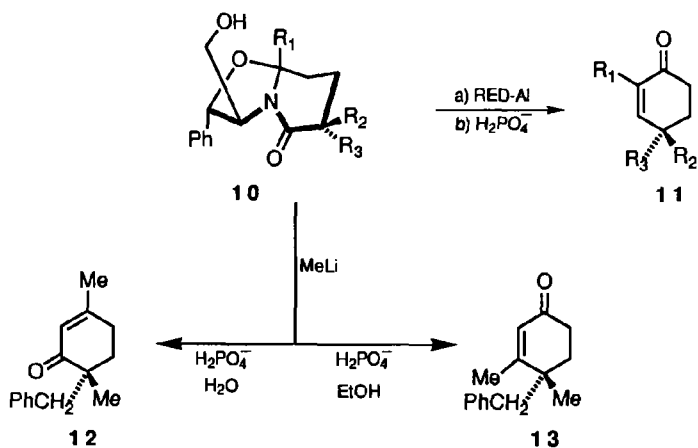


TABLE
CHIRAL 4,4-DIALKYL-CYCLOHEXENONES (11)^a

10				11			
R ₁	R ₂	R ₃	R ₁	R ₂	R ₃	% Yield	[α] _D
Me	Me	PhCH ₂	H	Me	PhCH ₂	53	-65.6°
Me	PhCH ₂	Me	H	PhCH ₂	Me	68	+64.8°
Me	PhCH ₂	Allyl	H	PhCH ₂	Allyl	47	+48.9°
Et	Me	PhCH ₂	Me	Me	PhCH ₂	66	-39.7°
Me	Ph	Me	H	Ph	Me	47	+122.2°

^aYields refer to reduction and hydrolysis of **10** to **11**. All products are 99% optically pure (see ref. 8).

Furthermore, in place of reduction of **10** it was possible to add organolithium reagents such that the resulting alkyl carbinolamine, after hydrolysis, gave either **12** or **13** depending upon hydrolysis conditions.⁶ In summary, these bicyclic lactams have provided a route to a variety of chiral, nonracemic cyclohexenones and cyclopentenones containing quaternary stereocenters.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Hexahydro-3-(hydroxymethyl)-8a-methyl-2-phenyl[2S,3S,8aR]-5-oxo-5H-oxazolo[3.2-a]pyridine: 5H-Oxazolo[3,2-a]pyridin-5-one, hexahydro-3-(hydroxymethyl)-8a-methyl-2-phenyl-, [2S-(2 α ,3 β ,8a β)]- (12); (116950-01-7)

(1S,2S)-(+)-2-Amino-1-phenyl-1,3-propanediol: 1,3-Propanediol, 2-amino-1-phenyl (9); (3306-06-7)

5-Oxohexanoic acid: Hexanoic acid, 5-oxo- (8,9); (3128-06-1)

Diisopropylamine (8); 2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

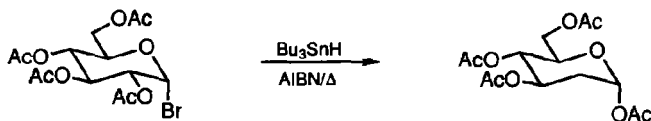
Ethyl iodide: Ethane, iodo- (8,9); (75-03-6)

Allyl bromide: 1-Propene, 3-bromo- (8,9); (106-95-6)

Red-Al: Aluminate(1-), dihydrobis(2-methoxyethanolato)-, sodium (8); Aluminate(1-), dihydrobis(2-methoxyethanolato-O,O')-, sodium (9); (22722-98-1)

Tetrabutylammonium dihydrogen phosphate: Ammonium, tetrabutyl-, phosphate (1:1) (8); 1-Butanaminium, N,N,N-tributyl-, phosphate (1:1) (9); (5574-97-0)

1,3,4,6-TETRA-O-ACETYL-2-DEOXY- α -D-GLUCOPYRANOSE
(α -D-arabino-Hexopyranose, 2-deoxy-, tetracetate)



Submitted by Bernd Giese and Kay S. Gröninger.¹

Checked by Matthew R. Sivik and Leo A. Paquette.

1. Procedure

A 1-L, round-bottomed flask equipped with a magnetic stirring bar, and a reflux condenser with a Claisen head on top fitted with a septum and dry nitrogen inlet, is charged with 20.6 g (50 mmol) of 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide (Note 1) and 400 mL of anhydrous toluene. The mixture is flushed with nitrogen and brought to reflux with a hot oil bath. A nitrogen atmosphere is maintained over the well-stirred reaction mixture during this and the ensuing steps. Meanwhile, a solution of 1.64 g (10 mmol) of azobisisobutyronitrile (AIBN) and 16.0 g (55 mmol) of tributylstannane in 90 mL of anhydrous toluene is prepared and filtered if necessary (Note 2). This solution is added to the refluxing, well-stirred reaction mixture during 6 hr by a syringe pump through a long needle which pierces the septum and ends at least 3 cm above the lower end of the cooling zone of the reflux condenser (Note 3). Ten minutes after all of the solution is added the reaction mixture is cooled and the solvent is removed with a rotary evaporator (bath 40°C); 100 mL of hexane and 100 mL of acetonitrile are added, and the resulting two-phase solution is stirred vigorously for 5 min and then transferred to a separatory funnel. The lower, acetonitrile layer is

separated and the hexane phase washed with 10 mL of acetonitrile (Note 4). This extraction of the combined acetonitrile solutions is repeated twice using 100 mL of hexane each time. The combined acetonitrile phases are then filtered and distilled (rotary evaporatory, bath 40°C). Coevaporation with 40 mL of hexane yields crude solid material which is dissolved in 120 mL of boiling tert-butyl methyl ether. Then 30 mL of hexane is added and the mixture left for 4 hr at room temperature. To complete crystallization of the product another 20 mL of hexane is added and the mixture is kept for 12 hr at 5°C. The long colorless needles are filtered and washed once with 30 mL of hexane/tert-butyl methyl ether (2:1) and two times with 30 mL of pentane to yield 13.2-13.4 g (79-81%) of 1,3,4,6-tetra-O-acetyl-2-deoxy- α -D-glucopyranose, mp 109-110°C [α]_D²⁰ +113° (C₂H₅OH, c 1.2).

2. Notes

1. This material was obtained from the Sigma Chemical Company and was recrystallized from diethyl ether/pentane before use. It can also be prepared by the procedure of Redemann, C. E.; Niemann, C. *Org. Synth., Coll. Vol. III* 1955, 11.

2. Azobisisobutyronitrile (AIBN) and tributylstannane were obtained from the Aldrich Chemical Company, Inc. The amount of AIBN can be reduced to 0.82 g (5 mmol) without affecting yields. A small excess (1.1 to 1.2 equiv) of tributylstannane must be used to ensure total consumption of starting material.

3. This method ensures that AIBN is not thermolized in the needle and that tributylstannane is diluted by the refluxing solvent before reaching the reaction mixture. It is also possible to add the tributylstannane solution by a dropping funnel (1 drop every 2 seconds) which replaces septum and syringe pump. This method gives

only slightly lower yields (75%) if the stannane solution runs down slowly on the glass surface of the condenser and does not enter the reaction mixture undiluted.

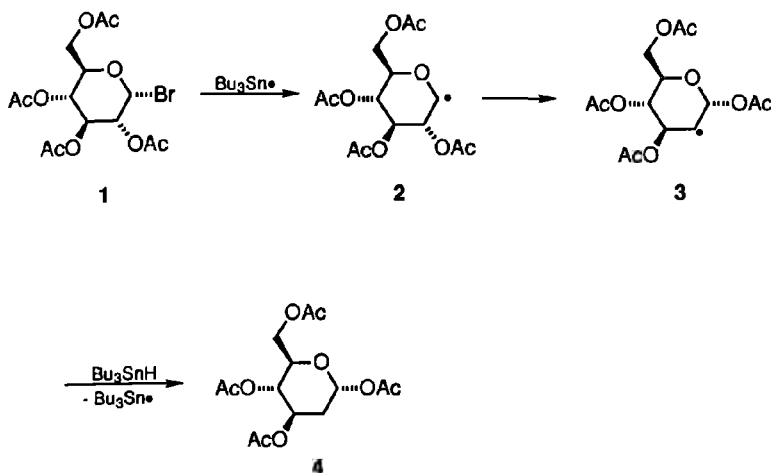
4. By this procedure most of the tributylbromostannane, and other stannyl compounds are removed. It is important to wait for complete separation of the phases.

5. The product is analytically pure, Anal., Calcd for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07. Found: C, 50.71; H, 6.25. 1H NMR (300 MHz, $CDCl_3$) δ : 1.97 (ddd, 1 H, H-2a; $J_{1,2a} = 3.7$, $J_{2a,2c} = 13.6$, $J_{2a,3} = 11.6$); 2.04, 2.05, 2.09, 2.14 (4 s, 12 H, acetyl); 2.28 (ddd, 1 H, H-2e, $J_{1,2e} = 1.4$, $J_{2e,3} = 5.3$); 4.00-4.11 (m, 2 H, H-5, H-6); 4.36 (m, 1 H, H-6"); 5.08 (t, 1 H, H-4, $J_{3,4} = J_{4,5} = 9.7$); 5.32 (ddd, 1 H, H-3); 6.26 (br d, 1 H, H-1).

6. Concentration of the mother liquors gives another 0.4-0.6 g of impure product which can be recrystallized from tert-butyl methyl ether/hexane to give another 0.3-0.5 g (2-3%) of analytically pure product.

3. Discussion

The main reaction step of this synthesis of 2-deoxy sugars is a radical rearrangement ($2 \rightarrow 3$).² Bromine abstraction from the glucosyl bromide **1** by tributyltin radicals yields glucosyl radical **2** that undergoes acetoxymigration and gives the rearranged radical **3**. This rearrangement is a stereoselective one-step reaction that occurs with rate coefficients of about 10^3 at 75°C in benzene.³ The driving force of the rearrangement $2 \rightarrow 3$ is the formation of the acetal structure at C-1 of **3**.⁴ Hydrogen abstraction from tributyltin hydride yields 2-deoxy sugar **4** and the tributyltin radical that starts another chain.



This rearrangement offers a general synthesis of α - and β -2-deoxy sugars with pyranoid and furanoid ring systems (Table).⁵

1. Institut für Organische Chemie, TH Darmstadt, Petersenstrasse 22, D-6100 Darmstadt, Germany.
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TABLE
Synthesis of 2-Deoxy Sugars
via Reductive Rearrangement of Glycosyl Derivatives⁵

Glycosyl Bromide	2-Deoxy Sugar	Yield(%)
		71
		70
		81
		65
		75

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1,3,4,6-Tetra-O-acetyl-2-deoxy- α -D-glucopyranose: D-arabino-Hexopyranose, 2-deoxy-, tetraacetate, α - (8); α -D-arabino-Hexopyranose, 2-deoxy-, tetraacetate (9); (16750-06-4)

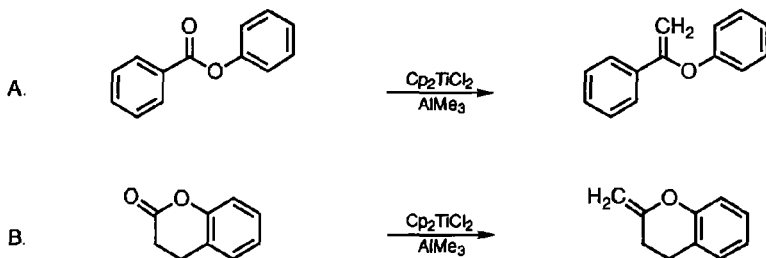
2,3,4,6-Tetra-O-acetyl- α -D-glucopyranosyl bromide: Glucopyranosyl bromide, tetraacetate, α -D- (8); α -D-glucopyranosyl bromide, 2,3,4,6-tetraacetate (9); (572-09-8)

Azobisisobutyronitrile: Propionitrile, 2,2'-azobis[2-methyl- (8); Propanenitrile, 2,2'-azobis[2-methyl- (9); (78-67-1)

Tributylstannane: Stannane, tributyl- (8,9); (688-73-3)

THE SYNTHESIS OF ENOL ETHERS BY METHYLENATION OF ESTER
1-PHENOXY-1-PHENYLETHENE AND 3,4-DIHYDRO-2-METHYLENE-
2H-1-BENZOPYRAN

(Ether, phenyl 1-phenylvinyl and 2H-1-Benzopyran, 3,4-dihydro-
2-methylene-)



Submitted by Stanley H. Pine,^{1a} Gia Kim,^{1b} and Virgil Lee.

Checked by Roger B. Ruggeri and Clayton H. Heathcock.

1. Procedure

A. *1-Phenoxy-1-phenylethene*. To a 250-mL round-bottomed flask (Note 1) equipped with a magnetic stirring bar is added 5.0 g (20.0 mmol) of titanocene dichloride [bis(cyclopentadienyl)titanium dichloride] (Note 2). The flask is fitted with a rubber septum through which a large-gauge needle is passed to flush the system with dry nitrogen. After the vessel has been thoroughly purged, the nitrogen line flowing to the needle is opened to a mineral oil bubbler and 20 mL of a trimethylaluminum solution (2.0 M in toluene, 40 mmol) is added by a nitrogen-purged syringe (Note 3). Methane gas evolved by the reaction is allowed to vent as the resulting red solution is stirred at room temperature for 3 days. The Tebbe reagent² thus formed is used in situ

by cooling the mixture in an ice-water bath (Note 4), then adding 4.0 g (20 mmol) of phenyl benzoate (Note 5) dissolved in 20 mL of dry tetrahydrofuran (Note 6) by syringe or cannula to the cooled stirring solution over 5-10 min. After the addition, the reaction mixture is allowed to warm to room temperature and is stirred for about 30 min. The septum is removed and 50 mL of anhydrous diethyl ether is added. To the stirring reaction mixture is gradually added 50 drops of an aqueous solution of 1 M sodium hydroxide over 10 to 20 min (Note 7). Stirring is continued until gas evolution essentially ceases; then to the resulting orange slurry are added a few grams of anhydrous sodium sulfate to remove excess water. The mixture is filtered through a Celite pad on a large coarse frit using suction and liberal amounts of diethyl ether to transfer the product and rinse the filter pad. Concentration of the filtrate with a rotary evaporator (Note 8) to 5-8 mL provides crude product, which is purified by column chromatography on basic alumina (150 g) eluting with 10% diethyl ether in pentane (Note 9). Fractions which contain product (Note 10) are combined and evaporated to give 2.69-2.79 g (68-70%) of the desired enol ether (Note 11) as a pale yellow oil.

B. 3,4-Dihydro-2-methylene-2H-1-benzopyran. Formation of the exo-methylene enol ether with dihydrocoumarin is carried out as in the foregoing procedure except that the reaction solution is cooled with a dry ice-acetone bath before addition of the lactone. From 3.0 g (20 mmol) of dihydrocoumarin (Note 5) is obtained 1.85-1.97 g (63-67%) of the product (Note 12) as a pale yellow oil, after column chromatography on basic alumina (150 g) eluting with 5% diethyl ether in pentane.

2. Notes

1. The checkers found that the acid liability of the enol ether products requires rigorous treatment of all glassware used for the reaction in order to avoid migration of the double bond in susceptible cases (e.g., dihydrocoumarin in Preparation B). Satisfactory results were obtained by treating the glassware sequentially with ethanolic 0.5 M solutions of hydrogen chloride and potassium hydroxide for approximately 1 hr, thoroughly rinsing with distilled water after each treatment and finally oven-drying. This protocol is also effective for removing stubborn deposits on the glassware used for the reaction.

2. Titanocene dichloride was purchased from Aldrich Chemical Company, Inc. and used without further purification. This compound is normally obtained as bright red crystals. If its purity is in question Soxhlet extraction using dichloromethane is usually effective; titanocene dichloride is slightly soluble in dichloromethane and slowly dissolves from insoluble materials present.

3. Trimethylaluminum was purchased from Aldrich Chemical Company Inc. and obtained as a 2.0 M solution in toluene sealed under nitrogen in a Sure/Seal bottle. Trimethylaluminum is pyrophoric and reacts violently with water and air; the syringe and needle used should be rinsed with toluene or hexanes immediately after addition. Note that the rinse, though dilute, contains pyrophoric material and should be handled accordingly.

4. Reaction with the ester is relatively exothermic. Sensitivity of the substrate-product to heating varies and should be considered for each particular compound. Phenyl benzoate can be methylenated at room temperature with no significant decrease in product yield. By contrast, dihydrocoumarin (Preparation B) gives no product under these conditions and must be methylenated at -78°C to obtain a good yield. For most substrates it is satisfactory to carry out reactions at 0°C .

5. Substrate esters were purchased from Aldrich Chemical Company, Inc. and used without further purification.

6. Tetrahydrofuran was freshly distilled from the sodium ketyl of benzophenone.

7. Evolution of methane can be quite vigorous so that the reaction vessel must be large enough to prevent bubbling over. If the aqueous solution is delivered slowly in 10-drop increments over the addition period a controlled quench of the reaction mixture is possible. Cooling slows gas evolution, but also greatly prolongs the hydrolysis step.

8. Methylene enol ethers are usually lower boiling than their ester precursors. Low molecular weight products can be easily lost in evaporation; therefore the toluene must be removed with care.

9. The checkers used Fisher Scientific basic alumina, Brockman activity I, 80-200 mesh. Neutral alumina and silica gel have also been used. Basic alumina minimizes the potential hazards of hydrolysis or proton-catalyzed isomerization of the carbon-carbon double bond in susceptible enol ethers. Gaseous trimethylamine has also been added to the eluent to minimize these problems during purification.

10. The checkers eluted the columns with a slight positive air pressure on the solvent reservoir to prevent formation of gas bubbles and cracks in the chromatographic medium. Fractions were collected in 25-mL test tubes (Note 1), analyzed by TLC on silica gel, eluting with the column solvent, and visualized with a phosphomolybdic acid solution. The checkers observed a nonvolatile hydrocarbon material (not substrate related) which was eluted in the fractions just prior to the products, which are quite nonpolar themselves and are eluted in the early fractions, ahead of any unreacted ester. Colored, metal-containing components usually remain near the top of the column, although some colored material may accompany the

product if much toluene remains in the sample or if the sample is applied to the column in a more polar solvent.

11. The spectral properties for 1-phenoxy-1-phenylethene are as follows: IR (film) cm^{-1} : 1600, 1495, 1290, 1230; ^1H NMR (250 MHz, CDCl_3) δ : 4.45 (d, 1 H, $J = 2.3$), 5.05 (d, 1 H, $J = 2.3$), 7.06-7.11 (m, 3 H), 7.29-7.38 (m, 5 H), 7.66-7.70 (m, 2 H).

12. While the submitters observed no complications, the checkers were unable, even after many trials, to obtain the dihydrocoumarin adduct completely free of what appears to be the product of double bond migration to give the endocyclic enol ether. Initial results were quite erratic. However, use of the glassware treatment described in Note 1, suggested by Professor Pine, has consistently provided the desired compound contaminated with only a few percent of the unwanted isomer. Spectral properties for the 3,4-dihydro-2-methylene-2H-1-benzopyran are as follows: IR (film) cm^{-1} : 1665, 1595, 1500, 1470, 1250, 990, 770; ^1H NMR (250 MHz, CDCl_3) δ : 2.57 (t, 2 H, $J = 6.5$), 2.80 (t, 2 H, $J = 6.5$), 4.14 (s, 1 H), 4.55 (s, 1 H), 6.85-6.92 (m, 2 H), 7.03-7.07 (m, 1 H), 7.11-7.18 (m, 1 H); impurity (partial) δ : 1.88 (bs, 3 H), 3.39 (bs, 2 H), 4.70 (bs, 1 H).

3. Discussion

The formation of carbon-carbon bonds through the condensation of carbonyl compounds with phosphoranes (the Wittig reaction) is a very useful method in organic synthesis.³ Allowing the convergence of a wide variety of substrates enables this reaction to provide considerable flexibility in product design. Yet, with limited exceptions,⁴ this process has not been effective for the transfer of methylene or alkylidenes to the carbonyl group of esters or other carboxylic acid derivatives. However, reaction of the titanium-aluminum complex (the Tebbe reagent)² described here does transfer a methylene to the carbonyl group of esters, effecting the conversion of an ester to an enol ether.⁵

The Tebbe reagent functions as a nucleophilic carbenoid in its reactions with carbonyl groups. The carbenoid is activated in the presence of a Lewis base which presumably complexes with the aluminum atom. Tetrahydrofuran is the Lewis base in the reactions described above. If the reaction is performed in the absence of added tetrahydrofuran, the carbonyl oxygen atom can function as a weak Lewis base, although the methylenation process is considerably slower.

Vinyl ethers have also been prepared by addition of alkoxides to acetylene,^{6,7,8} elimination from halo ethers and related precursors,^{6,8} and vinyl exchange reactions.⁸ Reaction of an electrophilic tungsten carbenoid with methylene phosphorane or diazomethane also produces vinyl ethers.⁹ Enol ethers have resulted from the reaction of some tantalum and niobium carbenoids with esters,¹⁰ and the reaction of phosphoranes with electrophilic esters.⁴

Methylenation using the titanium-aluminum complex converts a variety of esters to enol ethers in good yields.⁵ Lactones are converted to synthetically useful exomethylene enol ethers. Carbon-carbon double bonds do not interfere with the methylenation reaction, although functional groups containing acidic hydrogen atoms do consume the reagent and should be protected. The carbonyl group of aldehydes and ketones reacts in preference to the ester carbonyl group in the methylenation process,^{5b} but those groups can also be selectively protected.

Because of the expense of obtaining the Tebbe reagent in its pure form,¹¹ an in situ method for its preparation and use was developed.¹² The presence of the excess Lewis acidic by-product, dimethylaluminum chloride, in the in situ preparation may cause reactivity at other sites in the substrate or lower yields of desired products (e.g., 70% vs. 94% for Preparation A, and 65% vs. 85% for Preparation B).^{5b} However the overall simplicity of the method can be advantageous with readily obtained substrates.

1. (a) Department of Chemistry, California State University, Los Angeles, CA 90032; (b) Participant in the NIH-MBRS program.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-Phenoxy-1-phenylethene: Ether, phenyl 1-phenylvinyl (8,9); (19928-57-5)

3,4-Dihydro-2-methylene-2H-1-benzopyran: 2H-1-Benzopyran, 3,4-dihydro-2-methylene- (10); (74104-13-5)

Titanocene dichloride: Titanium, dichloro- π -cyclopentadienyl- (8); Titanium, dichlorobis(η^5 -2,4-cyclopentadien-1-yl)- (9); (1271-19-8)

Trimethylaluminum: Aluminum, trimethyl- (9); (75-24-1)

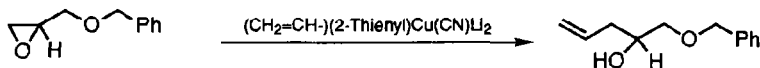
Phenyl benzoate: Benzoic acid, phenyl ester (8,9); (93-99-2)

Dihydrocoumarin: 2H-1-Benzopyran-2-one, 3,4-dihydro- (9); (119-84-6)

MIXED HIGHER ORDER CYANOCUPRATE-INDUCED EPOXIDE

OPENINGS: 1-BENZYLOXY-4-PENTEN-2-OL

(4-Penten-2-ol, 1-(phenylmethoxy)-)



Submitted by Bruce H. Lipshutz,¹ Robert Moretti, and Robert Crow.

Checked by Gary L. Bolton, Steven G. Toske, and James D. White.

1. Procedure

A 100-mL, two-necked, round-bottomed flask (Note 1), equipped with a stirring bar and a rubber septum is evacuated and flame-dried under vacuum, then flushed with dry argon. This process is repeated 3 times. Anhydrous tetrahydrofuran (36 mL, Note 2) and distilled thiophene (3.05 g, 2.91 mL, 36.3 mmol, Note 3) are injected via syringe and the resulting solution is cooled to -78°C . Butyllithium in hexanes (12.8 mL, 2.83 M, 36.3 mmol, Note 4) is added dropwise via syringe. The resulting light yellow solution is warmed to -20°C using a solid dry ice/carbon tetrachloride bath and stirred for 30 min.

A 500-mL, two-necked, round-bottomed flask equipped with a stirring bar and a rubber septum is charged with copper(I) cyanide (2.95 g, 33.0 mmol, Note 5). The flask is evacuated and gently flame-dried under vacuum (Note 6), then flushed with dry argon. The process is repeated 3 times. Anhydrous tetrahydrofuran (33 mL) is injected and the resulting slurry is cooled to -78°C . At this time, the previously prepared solution of 2-lithiothiophene in tetrahydrofuran (at -20°C) is added via cannula to the stirring slurry. At the end of the addition, the acetone-dry ice bath is

exchanged for an ice bath. After 5 min (Note 7), the flask is again placed in a dry ice-acetone bath. Vinylolithium in tetrahydrofuran (16.7 mL, 1.98 M, 33.0 mmol, Note 8) is added dropwise after 15 min. Then the -78°C bath is exchanged for an ice bath. After 5 min, the reaction mixture is recooled to -78°C and a cooled (-20°C) solution of benzyl 2,3-epoxypropyl ether (4.93 g, 30.0 mmol, Note 9) in anhydrous tetrahydrofuran (30 mL) is added to the cuprate solution via cannula over a period of 10 min. The reaction mixture is warmed to 0°C (Note 10). After 3 hr at 0°C, it is warmed to ambient temperature and stirred 1 more hr. It is then cooled to -78°C and poured on to a solution of saturated aqueous ammonium chloride (135 mL) and concentrated aqueous ammonium hydroxide (15 mL). The mixture is stirred for an additional 15 min while the temperature of the system is allowed to rise. The mixture is filtered through Celite. The flask and the filter cake are rinsed with tetrahydrofuran (2 x 20 mL). The tetrahydrofuran is evaporated using a rotary evaporator and the resulting aqueous layer is extracted with ethyl acetate (2 x 150 mL). Each organic layer is washed with water (75 mL) and brine (75 mL). The combined organic layers are dried over anhydrous sodium sulfate and concentrated with a rotary evaporator. The residue is purified by column chromatography on silica gel (Note 11), using a 6:1 mixture of petroleum ether and ethyl acetate as eluent (Note 12), to afford an oil (5.7 g, 29.6 mmol, 99%) which is distilled through a short-path distillation apparatus to give 4.20 g of an oil (26.1 mmol, 73%) (Note 13) as a colorless liquid, bp 85°C at 0.1 mm; IR (neat) cm^{-1} : 3400, 3070, 3030, 1640, 1100, 740, 700; ^1H NMR (CDCl_3) δ : 2.26 (t, 2 H, $J = 6.9$), 2.41 (d, 1 H, $J = 3.3$), 3.4-3.6 (m, 2 H), 3.90 (m, 1 H), 4.55 (s, 2 H), 5.1 (m, 2 H), 5.75-5.90 (m, 1 H), 7.33 (s, 5 H); mass spectrum, m/e (relative intensity): 192 (M^+ , 1.06), 92 (24.89), 91 (100); high resolution mass spectrum, Calcd for $\text{C}_{12}\text{H}_{16}\text{O}_2$: 192.1150. Found: 192.1161.

2. Notes

1. All glassware, needles and syringes are stored in an oven at 120°C overnight and assembled while hot.

2. Tetrahydrofuran is distilled from sodium-benzophenone before use.

3. Thiophene is purchased from the Aldrich Chemical Company, Inc. and distilled from calcium hydride before use.

4. Butyllithium in hexanes (2.5 M) is purchased from the Aldrich Chemical Company, Inc. and titrated with 2-pentanol in ether, using 1,10-phenanthroline as indicator before use.² Use of lower concentrations of butyllithium for the metalation of thiophene under these conditions results in incomplete lithiation.

5. Copper(I) cyanide is purchased from the Aldrich Chemical Company, Inc. and is dried in an Abderhalden apparatus at 56°C for ca. 2 days before use. *Caution: Copper(I) cyanide is very toxic.*

6. *Caution should be exercised during this operation. Overheating can result in partial decomposition of the copper(I) cyanide.*

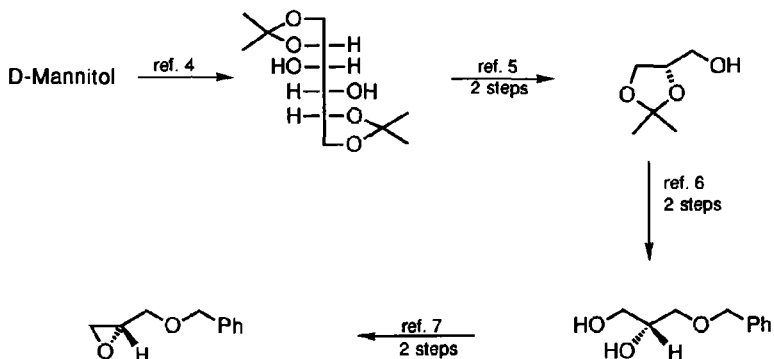
7. At this point, all of the copper(I) cyanide has been consumed and the reaction appears as a brown solution.

8. Vinyl lithium in tetrahydrofuran is purchased from Organometallics, Inc., and titrated² before use (see Note 4).

9. The starting material was prepared by the benzylation of glycidol, with benzyl bromide in tetrahydrofuran according to the following procedure: A 500-mL, two-necked, round-bottomed flask equipped with a stirring bar and a rubber septum is evacuated and flame-dried under vacuum, then flushed with dry argon. This process is repeated three times. A solution of distilled glycidol (4.0 g, 3.58 mL, 54 mmol, obtained from Aldrich Chemical Company, Inc. and distilled before use) in anhydrous tetrahydrofuran (139 mL) is injected via syringe and the resulting clear solution is

cooled to 0°C. Sodium hydride (2.24 g of a 60% dispersion in mineral oil, 56 mmol, obtained from Aldrich Chemical Company, Inc.) is added portionwise and the resulting gray mixture is stirred at 0°C for 30 min. Solid tetrabutylammonium iodide (0.21 g, 0.56 mmol, obtained from Aldrich Chemical Company, Inc.) is then introduced all at once. Distilled benzyl bromide (9.54 g, 6.63 mL, 55.8 mmol) is added (neat) dropwise via syringe. [Benzyl bromide was purchased from the Aldrich Chemical Company, Inc. and dried over MgSO₄, filtered, and distilled before use (*Caution: Benzyl bromide is light sensitive and is a potent lachrymator*).] The solution is stirred at 0°C for 5 min, then warmed to ambient temperature and stirred for 1 hr. The mixture is quenched with aqueous ammonium chloride and extracted with ethyl acetate (2 x 200 mL). Each organic phase is washed with water (100 mL) and brine (2 x 100 mL). The combined organic layers are dried over sodium sulfate and concentrated using a rotary evaporator. The remaining yellow residue is purified by flash chromatography,³ using a 5:1 mixture of petroleum ether and ethyl acetate as eluent, to afford chromatographically pure (±)-benzyl 2,3-epoxypropyl ether (7.34 g, 44.7 mmol, 83%) which can be distilled through a short-path distillation apparatus to give 6.52 g of the epoxide (39.7 mmol, 74%) as a colorless liquid, bp 105°C at 0.4 mm.

Optically active (S)-benzyl 2,3-epoxypropyl ether can be obtained in quantity in seven steps from D-mannitol according to literature procedures.⁴⁻⁷



10. At this point, the color of the solution turns from brown to light green, and darkens with time.

11. The technique of Still³ (flash chromatography) is used, with silica gel purchased from ICN Biomedicals (ICN Silica 21-63).

12. For TLC analyses, Merck silica gel F-254 TLC plates were used, with 1:1 petroleum ether-ether as eluent. Visualization was effected by spraying with a 5% phosphomolybdic acid in ethanol solution followed by heating at ca. 250°C on a hot plate. (R)-1-Benzyloxy-4-penten-2-ol has an R_f of ca. 0.35 in this solvent system.

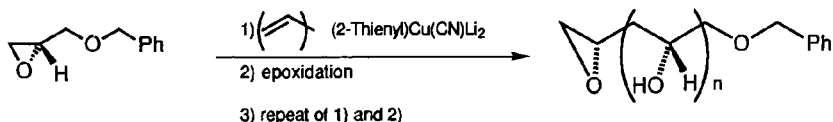
13. The checkers found that there was consistently 10-12% of 1-benzyloxyheptan-2-ol in the reaction mixture resulting from coupling of "residual" butyllithium (which forms $n\text{-Bu(Th)Cu(CN)Li}_2$) with the epoxide.

3. Discussion

This procedure is an illustration of the use of mixed, higher order (H.O.) cyanocuprates containing a non-transferable or "dummy" ligand for epoxide opening.⁸ H.O. cuprates of general stoichiometry $R_T(2\text{-thienyl})\text{Cu(CN)Li}_2$ can also be used to

has an array of 1,3-secondary hydroxyl groups, assumed to bear an all-syn relationship to each other, for which a synthetic strategy has been devised.¹²⁻¹⁴ Thus, a reiterative 2-step protocol involving epoxide opening with a H.O. vinylcyanocuprate, followed by stereoselective homoallylic alcohol epoxidation, reforms the functionality (i.e., an epoxide) from which it was originally derived (Scheme 2).

Scheme 2



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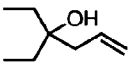
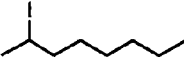
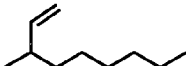
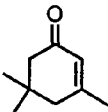
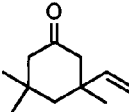
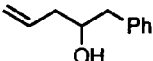
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-Benzyloxy-4-penten-2-ol: 4-Penten-2-ol, 1-(phenylmethoxy)- (9); (58931-16-11)
 Thiophene (8,9); (110-02-1)
 Butyllithium: Lithium, butyl- (8,9); (109-72-8)
 Copper(I) cyanide: Copper cyanide (8,9); (544-92-3)
 Vinyl lithium: Lithium, vinyl- (8); Lithium, ethenyl- (9); (917-57-7)
 Benzyl 2,3-epoxypropyl ether: Propane, 1-(benzyloxy)-2,3-epoxy- (8); Oxirane, [(phenylmethoxy)methyl]- (9); (2930-05-4)
 Glycidol: 1-Propanol, 2,3-epoxy- (8); Oxiranemethanol (9); (556-52-5)
 Benzyl bromide: Toluene, α -bromo- (8); Benzene, (bromomethyl)- (9); (100-39-0)
 Tetrabutylammonium iodide (8); 1-Butanaminium, N,N,N-tributyl-, iodide (9); (311-28-4)
 (S)-Benzyl 2,3-epoxypropyl ether: Propane, 1-(benzyloxy)-2,3-epoxy-, (S)- (8,9); (14618-80-5)
 D-Mannitol (8,9); (69-65-8)

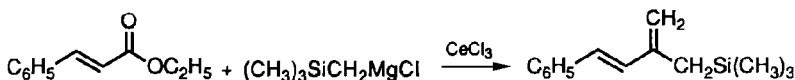
Table

Reactions of Various Substrates with (Vinyl)(2-thienyl)Cu(CN)Li₂.

Substrate	Equiv. of cuprate	Conditions	Product	Yield(%)
	1.20	THF/Et ₂ O room temp. 4 hr		71 ^a
	1.50	THF, 31° 18 hr		67 ^b
	1.10	THF/Et ₂ O 1.1 eq. BF ₃ -78°, 1 hr		98 ^b
	1.25	THF/Et ₂ O 0°, 1 hr		90 ^a

^aIsolated yield of chromatographically pure material. ^bBy quantitative GC analysis.

**THE CONVERSION OF ESTERS TO ALLYLSILANES:
TRIMETHYL(2-METHYLENE-4-PHENYL-3-BUTENYL)SILANE
(Silane, trimethyl (2-methylene-4-phenyl-3-butenyl)-)**



Submitted by William H. Bunnelle and B. A. Narayanan.¹

Checked by Jürgen Fischer and Ekkehard Winterfeldt.

1. Procedure

A 1-L, three-necked, round-bottomed flask with mechanical stirrer and vacuum outlet (Note 1) is charged with powdered cerium(III) chloride ($\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, 52.92 g, 0.142 mol) (Note 2). The flask is immersed to the necks in an oil bath and evacuated to 0.2 mm. The solid is agitated by stirring as the flask is heated to 150°C for 2 hr. After the flask is cooled to room temperature, it is vented to the atmosphere, and quickly purged with a stream of dry nitrogen for 2 min. At this stage, the flask is fitted with a low-temperature thermometer and a graduated 250-mL addition funnel containing 300 mL of dry tetrahydrofuran (THF) (Note 3), and capped with a rubber septum. Connection to a dry nitrogen line with a pressure relief bubbler is made via a needle through the septum. Tetrahydrofuran is run into the flask with good stirring, so that an even suspension results (Note 4). The white suspension is stirred at room temperature for 2 hr. Meanwhile, the addition funnel is charged with trimethylsilylmethylmagnesium chloride ($\text{Me}_3\text{SiCH}_2\text{MgCl}$, 1 M solution in ethyl ether, 142 mL, 0.142 mol) (Notes 5 and 6), transferred via stainless steel cannula. The contents of the flask are cooled to -65°C with a dry ice-2-propanol bath, and the

Grignard solution is added dropwise over a period of 40-50 min, so that the temperature of the reaction mixture remains below -60°C . The addition funnel is removed from the setup, with the septum/nitrogen inlet connected directly to the flask. After the cold mixture is stirred for 15 min more, ethyl cinnamate (10.32 g, 0.0586 mol) (Note 7) is added via syringe over a 2-3 min period. Stirring is continued as the flask is allowed to warm slowly to room temperature (Note 8). The off-white to beige reaction mixture is cooled to $<5^{\circ}\text{C}$ (ice-water bath) and quenched by the portion-wise addition of chilled 1 M hydrochloric acid (200 mL), so that the internal temperature remains below 20°C (Note 9). The layers are separated, and the aqueous phase is extracted twice with ethyl ether (100 mL each). The combined organic layers are washed with saturated sodium bicarbonate solution (Note 10), dried over sodium sulfate, and the solvents are removed at a rotary evaporator ($25^{\circ}\text{C}/60$ mm). The residual oil is transferred to a 100-mL, round-bottomed flask and distilled bulb-to-bulb (Note 11). The product (9.69-9.85 g, 76.5-78%) (Note 12) is collected at an air bath temperature of 110 - 112°C , 0.20 mm.

2. Notes

1. The vacuum outlet should be packed with glass wool, to prevent loss of significant quantities of cerium salt during the drying process. During some runs, cerium salts worked into the stirrer shaft bearing, causing it to bind. This problem could be avoided by placing a straight adapter tube between the bearing and the flask, to distance the bearing from the reaction mixture. The checkers found that sublimation of the cerium salt occurred in all their runs, but did not appear to affect the yield.

2. Cerium(III) chloride heptahydrate was purchased from Aldrich Chemical Company, Inc., and ground with a mortar and pestle just before use.

3. Tetrahydrofuran was freshly distilled under nitrogen from sodium and benzophenone. The (nominal) 250-mL funnel holds the entire volume of solvent.

4. On one occasion, when the solvent was added without stirring, the solid formed a hard cake on the bottom of the flask, and resisted attempts to bring it into suspension. The full 2 hr 'ageing' period is necessary for best results.

5. This clear, pale yellow solution was purchased from the Aldrich Chemical Company, Inc. The Grignard solution may be prepared from trimethylsilylmethyl chloride.² Take care to prevent air oxidation in opened bottles of the Grignard reagent -- these solutions deteriorate rapidly, and older samples are unsuitable for the present procedure.

6. The prescribed quantity of Grignard reagent (and cerium salt) is 25% more than stoichiometric. This excess is required to ensure complete consumption of the ester.

7. Ethyl cinnamate was purchased from Eastman Kodak Company, and was distilled at 110-111°C/0.75 mm before use.

8. Warming takes approximately 3 hr. The reaction is complete by this time and can be worked up. Alternatively, the mixture may be stirred at room temperature for at least 12 hr (overnight) without any deleterious effect on yield.

9. If the reaction is allowed to become warm, substantial protodesilylation of the product takes place to give 3-methyl-1-phenyl-1,3-butadiene. The aqueous workup should be carried out rapidly to minimize this side reaction. The use of hydrochloric acid has particular advantage since all of the salts dissolve facilitating the extractions.

10. Some residual salts precipitate during this operation, but do not pose any handling difficulty.

11. Gas chromatographic analysis (0.53-mm id x 10 m poly(dimethyl silicone) fused silica column, temperature programmed from 140°C to 220°C) indicates that this product is 98% pure, with <1% 3-methyl-1-phenyl-1,3-butadiene and 1-2% of a less volatile, unidentified component. The checkers could obtain a very pure product by normal vacuum distillation. They found the impurities to be higher boiling compounds.

12. This material has the following spectral data: IR cm^{-1} : 3068, 1593, 872, 853, 838; ^1H NMR δ : 0.01 (s, 9 H), 1.80 (br, s, 2 H), 4.83 (br, s, 1 H), 5.00 (d, 1 H, $J = 1$), 6.45 (d, 1 H, $J = 16$), 6.77 (d, 1 H, $J = 16$), 7.1-7.4 (m, 5 H); ^{13}C NMR δ : -1.2, 22.2, 114.8, 126.4, 127.3, 128.6, 128.7, 132.0, 137.4, 143.8; MS (m/e , %): 216 (40%), 73 (100%).

3. Discussion

Allylsilanes are exceptionally versatile compounds with a well-established function in organic synthesis.³ General methods for their preparation, then, are valuable. The method described here is effective for elaboration of esters to allylsilanes. The transformation is conceptually straightforward: twofold addition of a trimethylsilylmethyl metal species to the ester, followed by Peterson-type elimination from the resultant bis(trimethylsilylmethyl)carbinol, leads to the allylsilanes.

The Grignard reagent $\text{Me}_3\text{SiCH}_2\text{MgCl}$ has been used to effect this conversion with simple, unbranched esters, but the yields are only moderate (~50%) and the process fails completely for more sterically congested esters.⁴ In these cases, the α -silylketone intermediate resists further addition, instead suffering preferential enolization.⁵ The use of organocerium reagents to circumvent this difficulty has been developed by two groups.^{6,7} The reagent prepared from cerium(III) chloride and $\text{Me}_3\text{SiCH}_2\text{Li}$ is quite effective for conversion of acid chlorides to allylsilanes, but does not react efficiently with esters.⁶ Somewhat surprisingly in view of these results, a

mixture of cerium(III) chloride with $\text{Me}_3\text{SiCH}_2\text{MgCl}$ produces a powerful reagent for conversion of esters to allylsilanes in excellent yields.⁷ Some examples, for reactions carried out on a 1-mmol scale, are collected in the Table.⁷ Only the highly hindered methyl adamantanecarboxylate fails to react,

The protocol described above is a scaled-up modification of that reported earlier.⁷ The title compound has been prepared previously by a nickel-catalyzed cross-coupling,⁸ and by the organocerium/acid chloride route.⁶ The present procedure offers advantages in both convenience and yield compared to these other methods.

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Table

Ester	Alkylsilane	Yield (%)
		95
		90 ^a
		95
		77
		92
		0 ^b

^aStarting material and product each a 1:1 mixture of diastereoisomers.

^bStarting material recovered quantitatively.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

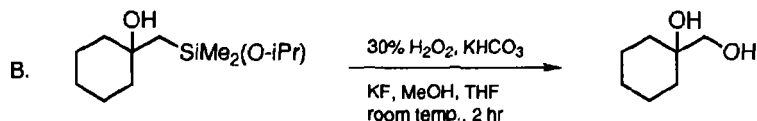
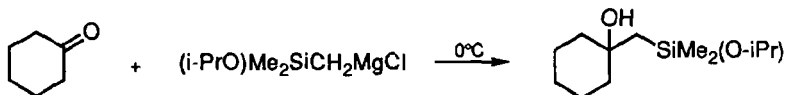
Trimethyl(2-methylene-4-phenyl-3-butenyl)silane: Silane, trimethyl(2-methylene-4-phenyl-3-butenyl)- (11); (80814-92-2)

Cerium(III) chloride heptahydrate: Cerium chloride heptahydrate (8); Cerium chloride (CeCl_3), heptahydrate (9); (18618-55-8)

Trimethylsilylmethylmagnesium chloride: Magnesium, [chloro[(trimethylsilyl)methyl]- (8,9); (13170-43-9)

Ethyl cinnamate: Cinnamic acid, ethyl ester (8); 2-Propenoic acid, 3-phenyl-, ethyl ester (9); (103-36-6)

NUCLEOPHILIC HYDROXYMETHYLATION OF CARBONYL COMPOUNDS:
1-(HYDROXYMETHYL)CYCLOHEXANOL
(Cyclohexanemethanol, 1-hydroxy-)



Submitted by Kohei Tamao, Neyoshi Ishida, Yoshihiko Ito, and Makoto Kumada.¹

Checked by Vinh D. Tran and Larry E. Overman.

1. Procedure

A. *1-[(Isopropoxydimethylsilyl)methyl]cyclohexanol*. A 500-mL, three-necked flask is equipped with a pressure-equalizing dropping funnel, magnetic stirrer, three-way stopcock, and a reflux condenser connected with a nitrogen bubbler. The flask is charged with magnesium turnings (2.43 g, 100 mg-atm) which are dried under a rapid stream of nitrogen with a heat gun. After the flask is cooled to room temperature, the rate of nitrogen flow is reduced. Several mL of a solution of (isopropoxydimethylsilyl)methyl chloride (16.67 g, 100 mmol) (Note 1) in dry tetrahydrofuran (THF) (120 mL) (Note 2) and about 50 μL of 1,2-dibromoethane are added. The mixture is stirred at room temperature and within a few minutes an exothermic reaction starts. The remaining solution is added dropwise at room

temperature over ca. 45 min at such a rate as to maintain a gently exothermic reaction. After the addition is complete, the tan-grey mixture is refluxed for 0.5 hr and then cooled to 0°C with an ice bath. A solution of freshly distilled cyclohexanone (7.36 g, 75 mmol) in dry THF (30 mL) is added dropwise with stirring over 30 min. The resultant mixture is stirred at 0°C for another 30 min (Note 3) and then hydrolyzed by dropwise addition of an aqueous 10% solution of ammonium chloride (100 mL) at 0°C over 10 min. The organic layer is separated. The aqueous layer is extracted with four 40-mL portions of diethyl ether. The combined organic layer and extracts are washed once with aqueous saturated sodium chloride, dried over magnesium sulfate, filtered into a 500-mL round-bottomed flask and concentrated with a rotary evaporator below room temperature (Note 4) at water aspirator pressure. A colorless oil remains (Note 5).

B. 1-(Hydroxymethyl)cyclohexanol. The 500-mL, round-bottomed flask which contains the crude 1-[(isopropoxydimethylsilyl)methyl]cyclohexanol is equipped with a magnetic stirrer and a thermometer, and is kept open to air throughout the reaction. The flask is charged with tetrahydrofuran (75 mL), methanol (75 mL) (Note 6), potassium hydrogen carbonate (7.5 g 75 mmol), and potassium fluoride (8.7 g, 105 mmol) (Note 7). To the stirred mixture is added 30% hydrogen peroxide (28.0 mL, 247.5 mmol) in one portion at room temperature. A somewhat cloudy organic layer and a milky-white heavy inorganic layer result. After several minutes an exothermic reaction begins which is controlled by intermittent, brief cooling with a water bath to maintain the temperature at 40-50°C (Note 8). After about 30 min the exothermic reaction ceases. The mixture is then stirred at room temperature for 2 hr (Note 9). The remaining hydrogen peroxide is decomposed by careful dropwise addition (Note 10) of an aqueous 50% solution of sodium thiosulfate pentahydrate (ca. 30 mL) with stirring over 30 min, during which time the temperature is maintained near 30°C by intermittent cooling with an ice bath (Note 11). A negative starch-iodide test is

observed (Note 12). A white precipitate forms and diethyl ether (ca. 100 mL) is added to ensure further precipitation. The mixture is filtered with suction and the filter cake is washed with three 20-mL portions of diethyl ether. The combined filtrate and washes are concentrated with a rotary evaporator at 50°C/water aspirator pressure until much of the water has been removed. The remaining oil is diluted with diethyl ether (ca. 200 mL), transferred to a separatory funnel and washed with saturated aqueous sodium chloride solution to remove the remaining water. The organic layer is separated, dried over magnesium sulfate, filtered, and concentrated with a rotary evaporator to give a colorless solid. The solid is dissolved in a 10:1 mixture of hexane - ethyl acetate (75 mL) at reflux, and the hot solution is filtered. The filtrate is allowed to cool to room temperature and finally is kept at 0°C for 2 hr. The crystals are separated with suction, washed with cold hexane/ethyl acetate (10:1, 10 mL), and dried under high vacuum at room temperature. There is obtained 7.54 g (77%) of 1-(hydroxymethyl)cyclohexanol as white crystals, mp 76.0-76.2°C (Notes 13, 14).

2. Notes

1. (Isopropoxydimethylsilyl)methyl chloride² is readily prepared from (chlorodimethylsilyl)methyl chloride by treatment with isopropyl alcohol (1.1 equiv) and triethylamine (1.1 equiv) in diethyl ether at room temperature (0.5 hr) and then at reflux temperature (0.5 hr). After filtration of the white salt, the filtrate is washed successively once with water, twice with 0.1 N hydrochloric acid, once with an aqueous 10% solution of sodium hydrogen carbonate and once with water, then dried over sodium sulfate. Filtration and distillation give the product in 80% yield, bp 65-67°C/50 mm, as an air-stable, colorless liquid. The checkers used commercially available material purchased from Aldrich Chemical Company, Inc.

2. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride under nitrogen (*Caution: See Org. Synth., Coll., Vol. V 1973, 976 for a warning regarding the purification of tetrahydrofuran. The checkers employed THF that had been purified by distillation from sodium and benzophenone.*).

3. The color of the mixture lightened slightly.

4. *Care must be taken not to raise the temperature since β -elimination of the β -hydroxysilane can result.*

5. The remaining oil appeared as one spot on silica gel TLC, $R_f = 0.8$ (hexane/ethyl acetate 1:1), and showed the following ^1H NMR spectrum (CDCl_3 , 300 MHz) δ : 0.19 (s, 6 H $\text{Si}(\text{CH}_3)_2$), 1.01 (s, 2 H, CH_2Si), 1.20 (d, 6 H, $J = 6$, $\text{CH}(\text{CH}_3)_2$), 1.38-1.75 (m, 10 H, $(\text{CH}_2)_5$), 3.5 (s, OH), 4.04 (septet, 1 H, $J = 6$, $\text{OCH}(\text{CH}_3)_2$).

6. Commercial reagent grade THF and methanol are used without further purification.

7. Potassium fluoride of anhydrous grade was purchased from Nakarai Chemicals. Ltd. This must be weighed quickly because it is highly hygroscopic. *The checkers used material purchased from Allied Chemical Company.*

8. The oxidation is so exothermic that the temperature reaches 60-65°C in 10 min if no external cooling is applied.

9. Completion of the oxidation was confirmed by TLC on silica gel: R_f of the product diol is 0.4 (hexane/ethyl acetate 1:1).

10. *Care must be taken not to add the thiosulfate solution in one portion; otherwise a violent, uncontrollable reaction might suddenly occur.*

11. The reaction temperature should be monitored carefully. If it falls below 10°C, the cooling bath should be removed to allow the mixture to warm to ca. 30°C.

12. If the test is still positive, thiosulfate solution should be added until a negative test is attained. *The checkers found EM Quant Peroxide Test Strips obtained from EM Science to be more sensitive than conventional KI-Starch test paper.*

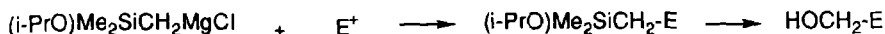
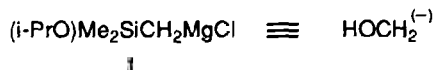
13. The reported melting point is 75-76°C.³

14. 1-(Hydroxymethyl)cyclohexanol exhibits the following spectral properties: ¹H NMR (300 MHz, CDCl₃) δ: 1.25-1.70 (broad m, 10 H, (CH₂)₅), 2.12 (s, 1 H, OH), 2.37 (t, 1 H, J = 6, OH), 3.45 (d, 2 H, J = 6, CH₂OH); IR (KBr) cm⁻¹: 3700-3020 (strong), 2920 (strong) 2845 (strong); Mass spectrum (24 eV): m/z (relative intensity) 130 (M⁺, 0.3), 99 (100), 81 (67); High resolution mass spectrum: Calcd for C₇H₁₄O₂, 130.0992; Found, 130.0969.

3. Discussion

This procedure for the preparation of 1-(hydroxymethyl)cyclohexanol is a modification of that reported by the submitters.⁴ While 1-(hydroxymethyl)cyclohexanol has been conventionally prepared from methylenecyclohexane by dihydroxylation^{5a} or from cyclohexanone in three steps through the cyanohydrin,^{5b} the present method consists of an alternative route from cyclohexanone via nucleophilic hydroxymethylation.

Although nucleophilic hydroxymethylating agents (hydroxymethyl anion synthons) or alkoxymethyl anions could be of great use in synthetic organic chemistry,⁶ only a few agents of this type have been developed so far. They include MeOH/TiCl₄/hν,⁷ Bu₃SnCH₂OH/BuLi,⁸ tert-BuOCH₂Li,⁹ HSiR₃/CO/Co₂(CO)₈,¹⁰ PhCH₂OCH₂Cl/SmI₂,¹¹ ArCO₂CH₂Li/LiAlH₄,¹² R₂BCH₂Li/[O],¹³ and (Me₃SiO)CH=C(OSiMe₃)₂.¹⁴ These methods are not as convenient or widely applicable as the method reported here. Two points deserve comment.

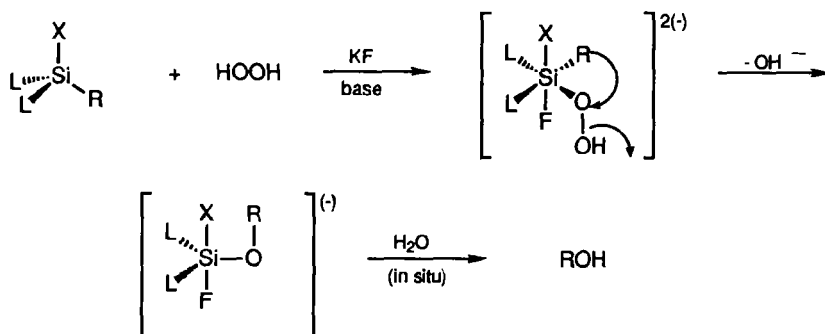


In addition to the (isopropoxydimethylsilyl)methyl Grignard reagent, (iso-PrO)Me₂SiCH₂MgCl (**1**), the (diisopropoxymethylsilyl)methyl counterpart, (iso-PrO)₂MeSiCH₂MgCl (**2**), has also been used as a nucleophilic hydroxymethylating agent.¹⁵ Despite labile alkoxy group(s) on silicon, the Grignard reagents are readily prepared in a normal manner in greater than 90% yields, and are sufficiently stable to be stored at room temperature for at least 2 days with little decrease in activity. The mono-isopropoxy Grignard reagent (**1**) is recommended as the reagent of first choice. Its precursor, (isopropoxydimethylsilyl)methyl chloride, is readily available at lower cost, and the reaction products, (iso-PrO)Me₂SiCH₂E, are more stable not only to aqueous work-up under weakly basic and acidic conditions, but also to silica gel chromatography.

The present method is based on the oxidative cleavage reaction of the silicon-carbon bond by hydrogen peroxide.¹⁶ The presence of at least one heteroatom on silicon is essential for the oxidative cleavage. Thus, the silicon-carbon bonds in hydro-, fluoro-, chloro-, alkoxy-, or amino-silanes are cleaved oxidatively to give the corresponding hydroxylated products. Although the oxidation may be performed in several ways, the following conditions (involving weak base and fluoride ion), may be the most efficient and most widely applicable: 30% H₂O₂ (1.2 equiv/Si-C bond), KHCO₃ (1 molar equiv), KF (2 molar equiv), MeOH/THF (1:1), room temperature. Under these conditions, the reaction usually occurs exothermically and is typically complete in several hours. Functional groups such as olefin, aldehyde, ketone, ester, amine, ether, ketal and tert-butyldimethylsiloxy groups, and furan, thiophene, and

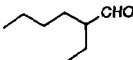
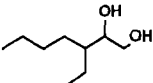
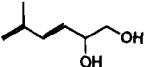
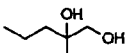
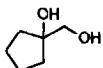
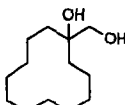
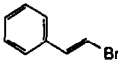
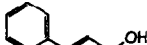
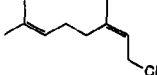
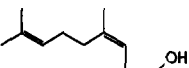
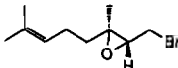
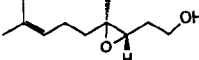
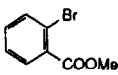
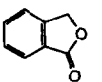
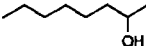
pyridine rings are stable under the oxidation conditions. The oxidation proceeds with complete retention of configuration at an sp^3 carbon. The oxidation has been considered to proceed through intramolecular migration of an organic group from silicon to the adjacent oxygen atom in penta- or hexacoordinate hydroperoxysilicon intermediates, as shown in Scheme 1 where X stands for a functional group. The oxidation has found a variety of synthetic applications.¹⁷

Scheme 1



Several representative examples of nucleophilic hydroxymethylation of aldehydes, ketones, organic halides, tosylates, and epoxides are summarized in Table I. The oxidation conditions given in the original literature are not necessarily optimum, and results may be improved by use of the oxidation method employed here. These results, summarized in Table I, demonstrate the general applicability of the silicon-based nucleophilic hydroxymethylation.

TABLE
Nucleophilic Hydroxymethylation of Aldehydes, Ketones,
Organic Halides, Alcohols, and Epoxides.^a

Starting Material	Product	Overall isolated yield (%)	Ref.
		67	4
		75	18
		86	4
		65	4
		63	4
		79	15
		87	15
		52	19
		86	15
		65	15
 (via tosylate)		67	20
		74	20

^a Introduction of the silylmethyl group into organic halides, tosylates, and epoxides is achieved by nickel-, palladium-, or copper-catalyzed cross-coupling reactions.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-(Hydroxymethyl)cyclohexanol: Cyclohexanemethanol, 1-hydroxy- (8,9);

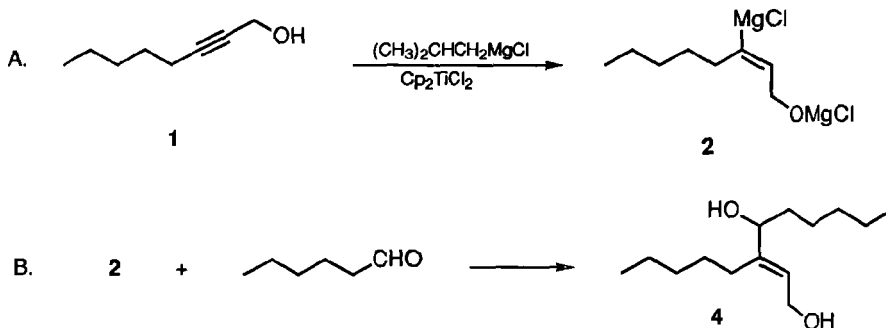
(15753-47-6)

(Isopropoxydimethylsilyl)methyl chloride: Silane, (chloromethyl)isopropoxydimethyl-

(9); (18171-11-4)

Cyclohexanone (8,9); (108-94-1)

**HYDROMAGNESIATION REACTION OF PROPARGYLIC ALCOHOLS:
(E)-3-PENTYL-2-NONENE-1,4-DIOL FROM 2-OCTYN-1-OL**



Submitted by Fumie Sato and Yuichi Kobayashi.¹

Checked by Zuliang Zhou and Ekkehard Winterfeldt.

1. Procedure

A. *The Grignard reagent 2.* A dry, 500-mL, three-necked, round-bottomed flask containing a magnetic stirring bar is equipped with a 100-mL pressure equalizing dropping funnel, a glass stopper, and a two-way stopcock to which is attached a T-piece connected at one end to a supply of nitrogen, and at the other to an oil bubbler (Note 1). The flask is charged with a solution of isobutylmagnesium chloride in ether (320 mL, 0.75 M, 240 mmol) (Notes 2 and 3) and immersed in an ice-water bath. Titanocene dichloride (1.3 g, 5.2 mmol) (Note 4) is added at once and the resulting solution is allowed to stir at 0°C for 10 min. A solution of 2-octyn-1-ol (**1**) (13.2 g, 105 mmol) (Note 5) in ether (30 mL) (Note 3) is placed in the dropping funnel and added dropwise to the flask over 20 min at 0°C. The solution is stirred at room temperature for 4 hr to complete the reaction, affording Grignard reagent **2** (Notes 6, 7, and 8).

B. (E)-3-Pentyl-2-nonene-1,4-diol (4). Half the amount of the Grignard reagent **2** prepared according to Procedure A is diluted with ether (160 mL) and cooled in an ice-water bath to 0°C. A solution of hexanal (9.25 g, 92.5 mmol) (Note 9) dissolved in ether (30 mL) (Note 3) is added through the dropping funnel over 30 min with efficient stirring. After the addition is complete, the solution is stirred at 0-5°C for 2 hr and then poured into saturated ammonium chloride solution (300 mL). The mixture is stirred at 0°C for 1 hr. The resulting precipitate is removed by filtration through a pad of Celite (70 x 24 mm) under reduced pressure and the precipitate is washed with ethyl acetate (100 mL). The organic layer is separated and the aqueous phase is extracted with ethyl acetate (150 mL). The combined organic layers are dried over magnesium sulfate and concentrated under reduced pressure to leave an oil which is purified by column chromatography on silica gel (Notes 10 and 11) to afford **4** (7.0-7.4 g, 59-62% yield) (Note 12).

2. Notes

1. Reactions A and B are carried out under a nitrogen atmosphere. The submitters used argon.

2. A solution of isobutylmagnesium chloride in ether was prepared using isobutyl chloride (13.8 g, 150 mmol), magnesium turnings (4.05 g, 165 mmol), and ether (175 mL) according to the procedure for the preparation of sec-butylmagnesium chloride reported by Gilman and Kirby.² The checkers found that this solution contained about 145 mmol of isobutylmagnesium chloride.

3. Ether and tetrahydrofuran were distilled from benzophenone ketyl under an argon atmosphere.

4. Titanocene dichloride was purchased from Aldrich Chemical Company, Inc., and used without further purification.

5. Alcohol **1** was prepared according to the procedure of Rickards and Weiler³ and distilled under reduced pressure (102-108°C/15 mm) before use. This material is also commercially available from Farchan Laboratories, Inc. The checkers obtained it from Lancaster Chemical Co.

6. The checkers found that Grignard reagent **2** could not be obtained quantitatively although all of the isobutylmagnesium chloride had reacted. The end point of the reaction was determined by TLC analysis of a small amount of reaction mixture after hydrolysis. 2-Octyn-1-ol (**1**) and (Z)-2-octen-1-ol (**3**), have R_F values of 0.53 and 0.47, respectively (using Silica Gel 60 F₂₅₄ pre-coated TLC aluminum sheets and benzene-ethyl acetate (1:1) as developing agent). If the reaction is not complete, an additional amount of titanocene dichloride should be added to the solution which is cooled again to 0°C before the addition.

7. The submitters report that, if this solution is poured into 1 N hydrochloric acid and ice and worked up in the usual manner, (Z)-2-octen-1-ol (**3**) may be obtained in 86% yield by distillation, bp 97-101°C (12 mm). This product has the following spectra: IR (neat) cm^{-1} : 3290, 1457, 1014; ^1H NMR (90 MHz, CCl_4 , $(\text{CH}_3)_4\text{Si}$, D_2O) δ : 0.88 (t, 3 H, $J = 6$), 1.05-1.57 (m, 6 H), 1.85-2.22 (m, 2 H), 4.03 (d, 2 H, $J = 5$), 5.27-5.65 (m, 2 H).

8. The submitters report that, if this solution is concentrated, then dissolved in tetrahydrofuran and treated with methyl iodide, (Z)-3-methyl-2-octen-1-ol (**5**) may be obtained after silica gel chromatography using hexane-ether as eluent. This product has the following spectra: IR (neat) cm^{-1} : 3305, 1447, 1000; ^1H NMR (90 MHz, CCl_4 , $(\text{CH}_3)_4\text{Si}$, D_2O) δ : 0.88 (t, 3 H, $J = 6$), 1.1-1.6 (m, 6 H), 1.68 (s, 3 H), 1.9-2.2 (m, 2 H), 3.99 (d, 2 H, $J = 6$), 5.29 (t, 1 H, $J = 6$).

9. Hexanal was used as supplied by Tokyo Kasei Kogyo Co., Ltd. (Japan). The checkers obtained it from Aldrich Chemical Company, Inc.

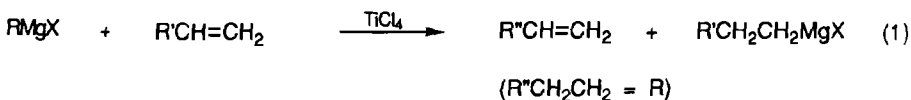
10. Silica gel (100-200 mesh) was purchased from Wako Pure Chemical Industries, LTD (Japan).

11. A silica gel column (225 g, 60 x 210 mm) is used with a mixture of benzene and ethyl acetate as an eluent [R_f value (benzene-ethyl acetate = 1:1): **3**, 0.47; **4**, 0.23]. Distillation of product **4** under reduced pressure caused partial decomposition (bp 120-155°C/0.25 mm).

12. Diol **4** has the following spectra: IR (neat) cm^{-1} : 3300, 1468, 1020; ^1H NMR (90 MHz, CDCl_3 , $(\text{CH}_3)_4\text{Si}$, D_2O) δ : 0.89 (t, 6 H, $J = 6$), 1.1-1.7 (m, 14 H), 1.9-2.2 (m, 4 H), 4.02 (m, 1 H), 4.20 (d, 2 H, $J = 6$), 5.63 (t, 1 H, $J = 6$). With D_2O exchange there is a change in the range of δ 1.9-2.2 (m, 2 H).

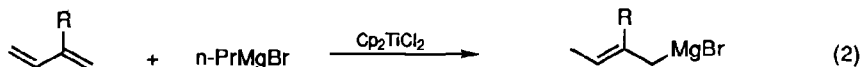
3. Discussion

In 1962 Cooper and Finkbeiner reported the titanium chloride (TiCl_4)-catalyzed exchange reaction of an alkyl Grignard reagent (RMgX) having β -hydrogen(s) with olefins (eq. 1).⁴ In this reaction, RMgX can be formally regarded as a source of HMgX which adds to the olefins, and hence this reaction is known as the hydromagnesiation reaction.

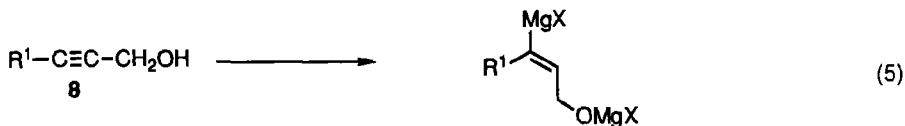
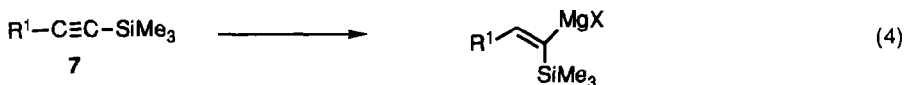
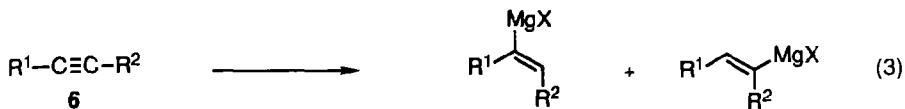


Since then, hydromagnesiation of other unsaturated hydrocarbons such as conjugated dienes and acetylenes has been investigated intensively.^{5,6} Hydromagnesiation of 2-alkyl substituted 1,3-butadienes has been shown to proceed

regiospecifically by using Cp_2TiCl_2 as a catalyst to afford the corresponding allylic Grignard reagent shown in eq. 2 quantitatively.⁷



Cp_2TiCl_2 -catalyzed hydromagnesiation of acetylenes with isobutyl Grignard reagents has also been shown to provide a convenient and practical method for preparation of various vinyl Grignard reagents. The acetylenes so far examined include 1,2-dialkylacetylenes **6** (eq. 3), 1-(trimethylsilyl)acetylenes **7** (eq. 4),⁸ propargyl alcohols **8** (eq. 5),⁹ and 3-(trimethylsilyl)propargyl alcohol (**9**) (eq. 6).¹⁰ Although the reaction occurs with low regioselectivity for unsymmetrical dialkylacetylenes **6**, high regioselectivity is attained in the case of **7**, **8**, and **9**. Acetylenes **6**, **7**, and **8** afford the corresponding vinylmagnesium halides in which HMgX adds in a syn pathway to the triple bond, while **9** affords the anti-addition product. In the latter case, hydromagnesiation follows the syn pathway to yield the corresponding (Z)-alkenyl Grignard reagent first, which, however, isomerizes rapidly under the reaction conditions to the (E)-alkenyl Grignard reagent. Since the hydromagnesiation reaction of **7**, **8**, and **9** proceeds highly regio- and stereoselectively, the reaction has become a powerful synthetic tool for utilization in organic syntheses. Some of the examples are given in the Table.



1. Department of Chemical Engineering, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan. Present address: Department of Biomolecular Engineering, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

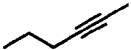
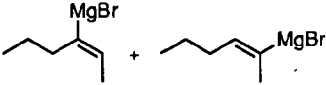
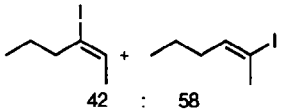
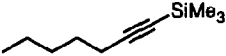
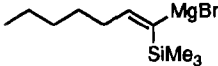
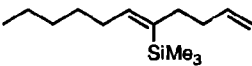
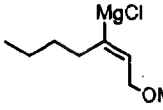
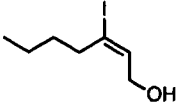
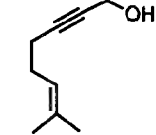
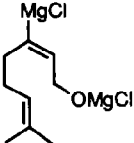
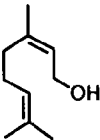
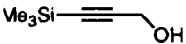
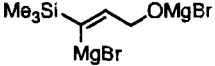
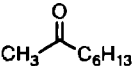
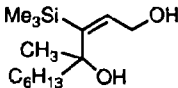
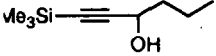
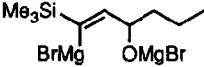
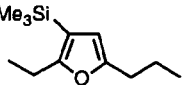
2-Octyn-1-ol (8,9); (20739-58-6)

Titanocene dichloride: Titanium, dichloro- π -cyclopentadienyl- (8);

Titanium, dichlorobis(η^5 -2,4-cyclopentadien-1-yl)- (9); (1271-19-8)

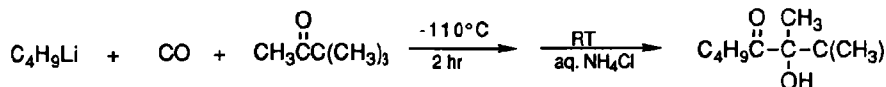
Hexanal (8,9); (66-25-1)

Table

Starting Acetylene	i-BuMgX X	Vinylmagnesium Halide	Electrophile	Product	Yield %	Ref.
	Br		I ₂	 42 : 58	70	8
	Br		 /CuI		86	11
	Cl		I ₂		78-86	9
	Cl		MeI		95	9
	Br				83	12
	Br		EtCN		86	13

**DIRECT NUCLEOPHILIC ACYLATION BY THE LOW TEMPERATURE,
IN SITU GENERATION OF ACYLLITHIUM REAGENTS; α -HYDROXY
KETONES FROM KETONES: 3-HYDROXY-2,2,3-TRIMETHYLOCTAN-
4-ONE FROM PINACOLONE**

(4-Octanone, 3-hydroxy-2,2,3-trimethyl-)



Submitted by Richard Hui and Dietmar Seyferth.¹

Checked by Hiroshi Koyano and Ryoji Noyori.

1. Procedure

A 2-L, three-necked flask was equipped with an overhead mechanical stirrer, a Claisen adapter which contained a low-temperature thermometer, and a no-air stopper which held a gas dispersion tube for the introduction of carbon monoxide (Note 1). The flask was charged with 400 mL each of tetrahydrofuran (THF) and diethyl ether, 100 mL of pentane, and pinacolone (7.92 g, 79.1 mmol) (Note 2). The reaction solution was cooled to -110°C (Notes 3 and 4) under an argon atmosphere and carbon monoxide (Note 5) was bubbled in for 30 min. Then a solution of butyllithium (2.53 N solution in pentane, 31.0 mL, 78.43 mmol) (Note 6) was added at 0.6-1.0 mL/min by means of a syringe pump (Note 7). The reaction mixture was orange after the addition had been completed. The reaction mixture was stirred at -110°C for 2 hr while the carbon monoxide stream was continued. The liquid nitrogen Dewar was removed, and the reaction mixture was allowed to warm to room temperature over the course of 1.5 hr, during which time the color changed to yellow.

The reaction mixture subsequently was quenched by the addition of 300 mL of saturated ammonium chloride solution, which resulted in a light yellow organic layer and a clear, colorless aqueous phase. The aqueous layer was separated and washed twice with 100 mL of pentane. The organic layers were combined, dried over anhydrous magnesium sulfate and filtered. The solvents were removed by fractional distillation (9" Vigreux column). The residue was distilled through a 7-cm jacketed column to give 9.7-10.8 g (67-73%) of 3-hydroxy-2,2,3-trimethyloctan-4-one, 97% pure by GLC, bp 120-122°C (30 mm), and n_D^{20} 1.442 (Note 8).

2. Notes

1. All glassware was dried for 15 hr in an oven at ca. 110°C and assembled while still warm.

2. Tetrahydrofuran (THF) and ether were distilled from sodium benzophenone ketyl. Pentane was distilled from lithium aluminum hydride and stored in bottles under a positive pressure of nitrogen. Pinacolone was distilled from potassium carbonate prior to use, bp 106°C (760 mm).

3. Total immersion type low temperature pentane thermometers (Kessler) were used to measure the temperature in the partial immersion mode. The readings are usually 7-8°C higher compared to the actual temperature under our reaction conditions. The temperatures reported here are all corrected by subtracting 7°C from the thermometer readings. The checkers used a Delta MC-20R digital thermometer (Sato Keiryoki Co., Japan). Temperature control is very important to obtain a satisfactory yield.

4. The temperature was controlled by moving a liquid nitrogen-filled Dewar flask up and down with a lab jack.

5. Carbon monoxide, purchased from Matheson Gas Products or Nihon Sanso Co., was used without further purification.

6. Butyllithium in pentane was purchased from Alfa Products, Morton/Thiokol Inc. and was titrated by the method of Gilman and Cartledge.^{2a} The checkers used a 1.56 N hexane solution purchased from Mitsuwa Chemical Co. after titration by the Kofron-Baclawski procedure.^{2b}

7. Orion Research Inc., Model 341 was used. Alternatively, if a syringe pump is not available, the organolithium solution may be added manually by syringe, very slowly and at a reasonably constant rate.

8. GLC conditions were as follows: 2 m x 5-mm glass column packed with 20% silicone SE-30 on chromosorb W AW; gas flow: 0.8 kg/cm²; temperature program 100-275°C at 6°C per minute; retention times: n-C₉H₂₀, 4.9 min; 3-hydroxy-2,2,3-trimethyloctan-4-one, 12.5 min. Spectral properties of the product are as follows: IR (thin film, NaCl) cm⁻¹: 3350-3580 (br, s, ν-OH), 2985 (s), 2872 (m), 1695 (s, ν C=O), 1480 (m), 1465 (s), 1462 (s), 1395 (s), 1220 (m), 1170 (m), 1125 (s), 1040 (s), 990 (m), 910 (m); ¹H NMR (270 MHz, CDCl₃) δ: 0.92 (t, 3 H, J = 7.3, CH₂-CH₃), 0.97 (s, 9 H, C(CH₃)₃), 1.33 (tq, 2 H, J = 7.3, 7.3, CH₂=CH₃), 1.34 (s, 3 H, CH₃), 1.60 (tt, 2 H, J = 7.6, 7.6, CH₂CH₂C(O)), 2.52 (dt, 1 H, J = 15.2, 7.6, a proton of CH₂C(O)), 2.60 (dt, 1 H, J = 15.2, 7.6, a proton of CH₂C(O)), 3.64 (s, 1 H, OH).

3. Discussion

In situ generated acyllithium reagents not only can acylate ketones, but also can acylate aldehydes,³ esters,⁴ lactones,⁵ isocyanates and isothiocyanates,⁶ carbodiimides,⁷ carbon disulfide and carbonyl sulfide,⁸ organic disulfides,⁹ and trialkylchlorosilanes.¹⁰ For reviews, see references 11 and 12. This direct, nucleophilic acylation procedure, when applicable, makes unnecessary the usually

applied method of "masked acyl anion equivalents" for nucleophilic acylation.¹³ The present procedure finds only very limited applicability in the case of aryllithium/CO systems,¹⁴ but seems to be generally applicable to alkylolithium systems.

1. Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139.
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13. See the leading reviews of masked acyl anion equivalents for examples and references: (a) Hase, T. A.; Koskimies, J. K. *Aldrichim. Acta* **1981**, *14*, 73; **1982**, *15*, 35; (b) Lever, O. W., Jr. *Tetrahedron* **1976**, *32*, 1943; (c) Albright, J. D. *Tetrahedron* **1983**, *39*, 3207; (d) Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357.

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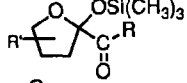
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

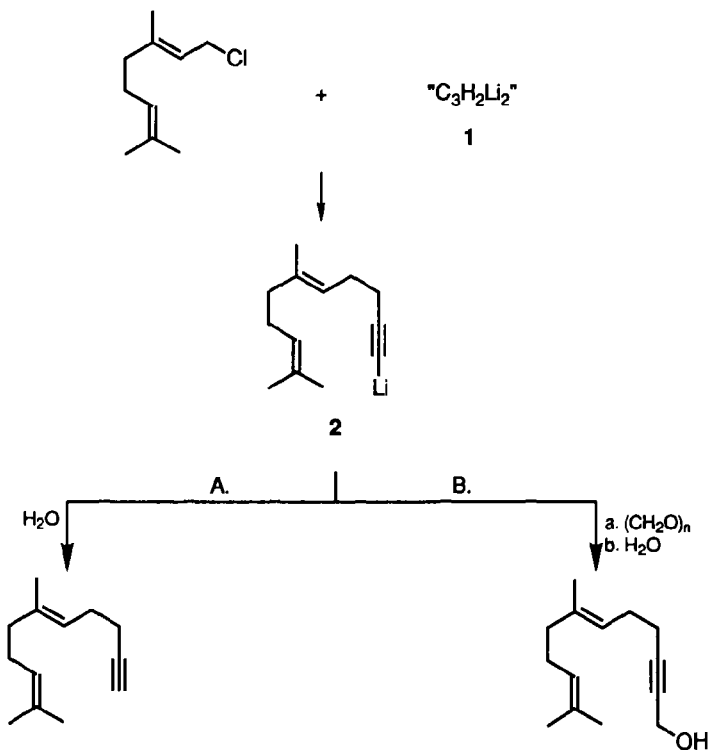
3-Hydroxy-2,2,3-trimethyl-4-octanone: 4-Octanone, 3-hydroxy-2,2,3-trimethyl- (11);
(85083-71-2)

Pinacolone: 2-Butanone, 3,3-dimethyl- (8,9); (75-97-8)

Table
Low Temperature, in situ, Direct Nucleophilic Acylation with the RLi/CO Reagent

Electrophile	Quench Reagent	Product	Reference
$(\text{CH}_3)_3\text{SiCl}$	H_2O	$(\text{CH}_3)_3\text{Si}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}$	10
$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}''$	H_2O	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{O}}{\parallel}{\text{C}}(\text{OH})\text{R}'\text{R}''$	3,4
$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{OR}''$	H_2O	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}'$	4
$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{NR}''_2$	H_2O	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}'$	12
$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{SR}''$	H_2O	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}'$	9
$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{H}$	H_2O	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}(\text{OH})\text{R}'$	3
	$(\text{CH}_3)_3\text{SiCl}$		5
$\text{R}'\text{SSR}'$	H_2O	$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{SR}'' + \text{RSH}$	9
$(\text{CH}_2)_n \begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{S} \end{array}$ $n = 4,5$	CH_3I	$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{S}(\text{CH}_2)_n\text{SCH}_3$	9
S_8	CH_3I	$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{SCH}_3$	9
COS	CH_3I	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{O}}{\parallel}{\text{C}}-\text{SCH}_3$	8
CS_2	CH_3I	$\text{R}'-\overset{\text{O}}{\parallel}{\text{C}}-\text{SCH}_3$	8
$\text{R}'\text{NCO}$	H_2O	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NHR}'$	6
$\text{R}'\text{NCS}$	H_2O	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{O}}{\parallel}{\text{C}}(\text{S})-\text{NHR}'$	6
	CH_3I	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{O}}{\parallel}{\text{C}}(\text{NR}')-\text{SCH}_3$	6
$\text{R}'\text{N}=\text{C}=\text{NR}'$	H_2O	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{O}}{\parallel}{\text{C}}(\text{NR}')-\text{NHR}'$	7
$\text{Fe}(\text{CO})_5$		$(\text{OC})_4\text{Fe}=\overset{\text{O}^-}{\text{C}}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R} \quad (\text{CH}_3)_4\text{N}^+$ (R = <i>tert</i> -Bu)	15

**PROPARGYLATION OF ALKYL HALIDES: SYNTHESIS OF
(E)-6,10-DIMETHYL-5,9-UNDECADIEN-1-YNE AND
(E)-7,11-DIMETHYL-6,10-DODECADIEN-2-YN-1-OL
(5,9-Undecadien-1-yne, 6,10-dimethyl-, (E)-) and
(6,10-Dodecadien-2-yn-1-ol, 7,11-dimethyl-, (E)-)**



Submitted by John Hooz,^{1*} Jorge Cabezas,² Sergio Musmanni,² and Jose Calzada.^{2*}

Checked by Hanno Wild, Andreas Weier, and Larry E. Overman.

1. Procedure

Caution! Allene and ethyl ether are highly volatile and flammable. Paraformaldehyde is a noxious material. The entire operation should be conducted in an efficient fume hood.

A. *(E)-6,10-Dimethyl-5,9-undecadien-1-yne.* An oven-dried (Note 1), 1-L, three-necked, round-bottomed flask is equipped with a large magnetic stirring bar (Note 2), a 250-mL pressure-equalizing addition funnel capped by a rubber septum (Note 3), a dry ice condenser capped by a rubber septum, and a rubber septum (capping the central neck) bearing a stainless steel cannula which serves as an argon inlet. The flask is charged with 190 mL of anhydrous ethyl ether (Note 4) and cooled to ca. -78°C using a dry ice-acetone bath. On a separate assembly (Note 5), allene gas (d at -40°C = 0.67 g/mL) from a compressed gas cylinder (Note 6) is condensed into a dry, 100-mL Pyrex graduated cylinder equipped with a 24/40 standard taper joint attached to a Claisen adapter and dry ice condenser (containing a slurry of dry ice-acetone) and cooled to -78°C with a bath of dry ice-acetone (Note 7). After 22.5 mL (375 mmol) of liquid allene has been collected, the adapter and condenser are removed and the graduated cylinder is capped with a rubber septum through which is inserted a cannula. The other end of this cannula is inserted through the rubber septum on the central neck to reach just below the surface of the cooled solvent. The allene is then transferred to the reaction vessel by removing the cylinder from the cooling bath. The temperature of the reaction vessel is maintained at -78°C, and a solution of 190 mL of 1.37 M butyllithium (260 mmol) in hexane (Note 8) is added dropwise over 1 hr through the addition funnel which is then rinsed with 5 mL of dry ether. The reaction mixture is allowed to warm gradually (over ca. 30 min) to -15°C and the white precipitate that forms is stirred an additional 15 min under an argon atmosphere. A solution of 12.9 g (75 mmol) of geranyl chloride (Note 9) in 40 mL of

dry ether is added dropwise over 30 min through the addition funnel while maintaining the temperature at -15°C . Then the stirred mixture is allowed to warm to room temperature over 1 hr (Note 10). The resulting white suspension containing the lithium acetylide **2** is carefully poured into 450 mL of ice water slurry, the aqueous layer is saturated with sodium chloride, and the product is extracted with four 100-mL portions of ether. The combined extracts are dried over anhydrous magnesium sulfate, the drying agent is removed by filtration, and the solvent is distilled at atmospheric pressure using a 25-cm Vigreux column. The residue is distilled through a short-path distillation apparatus to afford 10.5-11.2 g (79-89% yield) of (E)-6,10-dimethyl-5,9-undecadien-1-yne, bp $103-107^{\circ}\text{C}$ (10 mm) (Note 11).

B. (E)-7,11-Dimethyl-6,10-dodecadien-2-yn-1-ol. To the suspension containing the acetylide intermediate **2**, as prepared in part A, is added 14 g (460 mmol) of paraformaldehyde (Note 12) in portions (Note 13) over 10 min (Note 14). After stirring the mixture for 24 hr, the resulting suspension is poured into 450 mL of ice-cold water (Note 15), the aqueous layer is saturated with sodium chloride, and the product is extracted with four 100-mL portions of ether. The combined organic extracts are dried over magnesium sulfate, the drying agent is removed by filtration, and the solvent is removed at room temperature on a rotary evaporator. The residue is distilled through a short-path distillation apparatus to provide a forerun of 2-butyne-1-ol (bp $42-46^{\circ}\text{C}$, 6 mm), followed by 10.5 g (68% yield) of (E)-7,11-dimethyl-6,10-dodecadien-2-yn-1-ol as a colorless liquid, bp $120-124^{\circ}\text{C}$ (0.5 mm) (Note 16).

2. Notes

1. All glassware is dried in an oven at 125°C and assembled while warm.
2. Although the reaction mixture will become heterogeneous, mechanical stirring is unnecessary on this scale.

3. A stainless steel cannula inserted through this septum is connected by means of tygon tubing to a mercury bubbler.

4. Ethyl ether is freshly distilled from the sodium ketyl of benzophenone.

5. This is an adaptation of the method used to condense methyl chloride, illustrated in Figure 1 of an *Organic Syntheses* procedure (Lusch, M. J.; Phillips, W. V.; Sieloff, R. F.; Nomura, G. S.; House, H. O. *Org. Synth., Coll. Vol. 7*, **1990**, 347).

6. The submitters used allene purchased from Matheson Gas Products, Inc. The checkers found that an old lecture bottle of allene from this source gave unsatisfactory results, affording a crude product that contained up to 20% of unchanged geranyl chloride. Other lecture bottles of allene from Matheson or Pfaltz and Bauer were satisfactory.

7. All temperatures recorded are external bath temperatures.

8. A solution of butyllithium in hexane was purchased from Foote Mineral Company. Before use the concentration is determined by titration according to the procedure of Watson and Eastham.³

9. Geranyl chloride was prepared by treating geraniol, available from Aldrich Chemical Company, Inc., with carbon tetrachloride and triphenylphosphine according to an *Organic Syntheses* procedure.⁴

10. If dienyne product containing less than 1% of geranyl chloride is required, the checkers suggest the following treatment at this point to destroy any remaining geranyl chloride: The addition funnel is removed and a gentle stream of argon is bubbled through the stirred reaction mixture for 15 min to remove excess allene. Additional butyllithium (40 mmol in hexane) is added and the resulting mixture is stirred for 3 hr at room temperature prior to hydrolytic work up. If this modification is employed the subsequent hydrolysis step should be done slowly. The Erlenmeyer flask (1 L) containing the ice/water mixture is best cooled externally with an ice bath during the hydrolysis.

The checkers also report that (E)-6,10-dimethyl-5,9-undecadien-1-yne containing < 1% geranyl chloride is produced in 78-90% yield when 2.0 mmol of butyllithium per mmol of allene is employed.

11. Capillary GC analysis of the product using a 25-m fused silica DB-5 column shows the presence of 5% geranyl chloride which is eluted at a slightly shorter retention time than the enyne product. Similar analysis of the product produced (in 89% yield) by the modification reported in Note 10 showed that the product was > 96% pure and contained < 1% of geranyl chloride. Spectral properties for (E)-6,10-dimethyl-5,9-undecadien-1-yne are: IR (thin film) cm^{-1} : 3312, 2119, 1665; ^1H NMR (300 MHz, CDCl_3) δ : 1.58 (s, 3 H), 1.60 (s, 3 H), 1.66 (s, 3 H), 1.97-2.14 (m, 4 H), 2.22 (narrow m, 4 H), 5.11 (m, 2 H), 5.19 (m, 1 H).

12. Paraformaldehyde is dried over P_2O_5 in a vacuum desiccator for 24 hr prior to use.

13. The dropping funnel is removed and replaced by a 250-mL Erlenmeyer flask containing the paraformaldehyde. This is connected to the reaction vessel by rubber tubing. The cannula previously attached to the mercury bubbler is inserted through the septum of the dry ice condenser.

14. The reaction with paraformaldehyde has an induction period of approximately 7-10 min, when the solvent suddenly begins to boil. The dry ice condenser should be kept charged with dry ice-acetone to avoid loss of solvent.

15. In some runs the checkers found that the slurry became too thick to stir. In these cases, the ice-cold water (450 mL) was added to the reaction flask while stirring the solid mass with a large spatula. The final yield of the alcohol product was similar in these runs. Alternatively the reaction flask can be mechanically stirred.

16. The purity of the product was determined to be 92-94% by capillary GLC analysis using a fused silica 25-m x DB-5 column, 70-280°C (10°C/min). The spectral properties of the product are as follows: IR (thin film) cm^{-1} : 3334, 2287, 2224, 1670

and 1020; ^1H NMR (500 MHz, CDCl_3) δ : 1.50 (t, 1 H, $J = 10.8$), 1.60 (s, 3 H), 1.61 (s, 3 H), 1.68 (s, 3 H), 1.99 (m, 2 H), 2.07 (m, 2 H), 2.22 (narrow m, 4 H), 4.25 (d, 2H, $J = 10.8$), 5.09 (m, 1 H), 5.16 (m, 1 H). Vinylic signals for minor impurities are apparent at δ 4.7-4.9.

3. Discussion

The highly-useful three-carbon homologation, $\text{RX} \rightarrow \text{RCH}_2\text{C}\equiv\text{CH}$, often employed in isoprenoid-related syntheses (e.g., sirenin,⁵ C_{18} -Cecropia juvenile hormone,⁶ 16,17-dehydropregesterone⁷) is frequently difficult to accomplish cleanly because of the tendency of ambident propargylic nucleophiles, $\text{R-C}\equiv\text{C-CH}_2\text{M}$, **3**, to produce troublesome mixtures of both the allenic and acetylenic products.^{8,9,10} Propargyl aluminates **3** [$\text{M}=\text{Al}(\text{i-C}_4\text{H}_9)_3$], for example, couple with allyl bromide to produce mainly the corresponding allene (< 4% acetylene), whereas the analogous borate complex **3** [$\text{M}=\text{B}(\text{sec-C}_4\text{H}_9)_3$] produces an 83:17 mixture of the corresponding allene:acetylene.¹¹ The "propargyl" Grignard reagent¹² also couples with allylic halides^{7,13,14} to produce acetylenic-allenic mixtures, for which a separation procedure has been developed based on trimethylsilylation of the crude product mixture.¹³ An indirect procedure employing lithio-1-trimethylsilylpropyne initially produces the trimethylsilyl-protected acetylene (50-55%), from which the required homologated alkyne is liberated by reaction with ethanolic silver nitrate followed by sodium cyanide.¹⁵ 1,3-Dilithiopropyne in either tetramethylethylenediamine or 1,4-diazabicyclo[2.2.2]octane is reported to couple with simple halides¹⁶ to form acetylenes in moderate yield, although it fails to couple cleanly with allylic halides.¹⁷

The present procedure, based on the controlled lithiation of allene, produces the operational equivalent of a propargyl dianion **1** ($\text{C}_3\text{H}_2\text{Li}_2$), and provides a convenient single-step route to propargylated derivatives. Lithiation of allene is

deceptively complex, and the extent of metalation (i.e., mono-, di-, tri-, tetra-) and the regiochemical outcome of subsequent alkylation (allenic vs. acetylenic) is highly dependent on reaction conditions. Metalation by butyllithium (1 equiv, THF, -70°C) followed by alkylation with octyl iodide produced an 87:13 mixture of the corresponding allene and acetylene,¹⁸ whereas an allene:C₄H₉Li ratio of 1:2 (THF, -50°C) followed by trimethylsilylation, produced a mixture comprised of mono-, di-, tri-, and tetra-silylated products.¹⁹ In the current procedure, the solvent ratio (v/v) of ether:hexane of 1:1, as well as the stoichiometry and temperature, were empirically determined, and under these conditions there was no detectable evidence (NMR, GLPC) of isomeric allene formation in any of the alkylations examined, either for simple or allylic halides.²⁰ An additional advantage is that the initially-formed lithium acetylide intermediate (e.g., **2**) may be further transformed to other useful functional derivatives in situ, as illustrated by the hydroxymethylation procedure.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

(E)-6,10-Dimethyl-5,9-undecadien-1-yne: 5,9-undecadien-1-yne, 6,10-dimethyl-, (E)- (8,9); (22850-55-1)

(E)-7,11-Dimethyl-6,10-dodecadien-2-yn-1-ol: 6,10-Dodecadien-2-yn-1-ol, 7,11-dimethyl-, (E)- (8,9); (16933-56-5)

Allene (8); 1,2-Propadiene (9); (463-49-0)

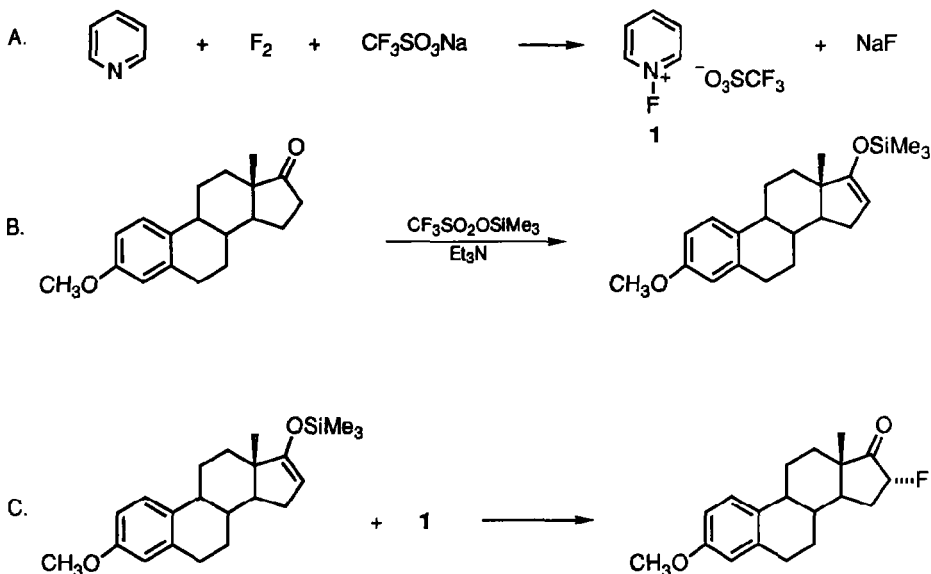
Butyllithium: Lithium, butyl- (8,9); (109-72-8)

Geranyl chloride: 2,6-Octadiene, 1-chloro-3,7-dimethyl-, (E)- (8,9); (5389-87-7)

Paraformaldehyde $(\text{CH}_2\text{O})_n$: Poly(oxymethylene) (8,9); (9002-81-7) [Supplied by Alfa]
or Paraformaldehyde $(\text{CH}_2\text{O})_x$ (9); (30525-89-4) [Supplied by Aldrich, Fischer, Fluka]

N-FLUOROPYRIDINIUM TRIFLATE:
AN ELECTROPHILIC FLUORINATING AGENT

(Pyridinium, 1-fluoro-, salt with trifluoromethanesulfonic acid (1:1))



Submitted by Teruo Umemoto,^{1a} Kyoichi Tomita,^{1a,b} and Kosuke Kawada.^{1a,b}

Checked by Shlomo Rozen and Bruce E. Smart.

1. Procedure

Caution! Molecular fluorine is a very toxic and corrosive gas. The following reaction should be carried out in an efficient fume hood, and the experimenter should be familiar with the precautions necessary for safe handling of fluorine.² Since molecular fluorine diluted with an inert gas is much safer to handle than pure fluorine,

the use of a fluorine/nitrogen mixture comprising no more than 20% fluorine is recommended.

A. *N*-Fluoropyridinium triflate (1). The reaction is carried out in the apparatus shown in Figure 1. The pressure regulator on the cylinder containing a mixture of 20% fluorine/80% nitrogen (Note 1), and the pressure gauge and flowmeter on the fluorine line are specifically designed for fluorine service (Note 2). The fluorine and nitrogen cylinders, pressure regulators, flowmeters, valves, and filters are connected with stainless steel tubing. The Pyrex glass reaction vessel is connected to the metal tubing via Viton® tubing, and the fluorine gas is introduced into the vessel through a Pyrex glass tube (7 mm o.d.). The gas outlet from the reaction vessel is connected to a granular alumina trap which consumes molecular fluorine.

The 300-mL, round-bottomed reaction flask is charged with 4.74 g (0.06 mol) of pyridine (Note 3), 10.3 g (0.06 mol) of sodium triflate (Note 4), and 80 mL of dry acetonitrile (Note 5). The system is purged with nitrogen, and the reaction mixture is chilled and maintained at -40°C. The flow of dilute fluorine is started, and the flow rates from the nitrogen and fluorine cylinders are adjusted to introduce a 10% fluorine/90% nitrogen mixture at a rate of 90 mL/min just above the surface of the rapidly stirred solution (Note 6). When a total of 2.7 L of fluorine (0.12 mol) is introduced (Note 7), the flow of fluorine is discontinued and nitrogen only is flowed through the system at a rate of 45 mL/min for 30 min while keeping the reaction mixture at -40°C. The reaction mixture is then warmed to room temperature and filtered through a pad of Celite to remove the sodium fluoride. The filtrate is concentrated to dryness with a rotary evaporator without heating. The crystalline residue is washed with 30 mL of dry ethyl acetate to give 11.0-12.0 g (74-81%) of crude product, mp 178-181°C. The crude material is dissolved in 18 mL of dry acetonitrile at room temperature, and 36 mL of dry diethyl ether is added. The

precipitated crystals are collected by filtration under nitrogen (Note 8) to give 10.0-10.3 g (68-70%) of pure N-fluoropyridinium triflate, mp 182°C (Notes 9, 10, and 11).

B. 3-Methoxy-17-trimethylsiloxy-1,3,5(10),16-estratetraene. A 125-mL, two-necked, round-bottomed flask equipped with a reflux condenser and a magnetic stirrer is purged with argon and charged with 6.8 g (0.024 mol) of estrone 3-methyl ether (Note 12), 50 mL of dry benzene, and 4.0 mL (2.9 g, 0.029 mol) of triethylamine. The solution is stirred, 4.9 mL (5.6 g, 0.025 mol) of trimethylsilyl triflate (Note 13) is added through a syringe, and the mixture is refluxed for 1.5 hr. The reaction mixture is allowed to cool to room temperature, whereupon it separates into two layers. Dry hexane (40 mL) is added, and the upper hexane-benzene layer is separated, washed successively with saturated sodium bicarbonate and water, and then dried over magnesium sulfate. The drying agent is removed by filtration, and the filtrate is transferred to a 125-mL, round-bottomed, tared flask. The solution is evaporated to a constant weight with a rotary evaporator, initially at water-aspirator pressure and then at 0.5-1 mm, to leave 8.6 g (100%) of pale yellow enol trimethylsilyl ether. This material is used immediately in Part C without purification (Note 14).

C. 16 α -Fluoro-3-methoxy-1,3,5(10)-estratrien-17-one (16 α -fluoroestrone 3-methyl ether). The 125-mL, round-bottomed flask containing the enol silyl ether from Part B is purged with argon, and 50 mL of dry dichloromethane is added. N-Fluoropyridinium triflate (1) (6.5 g, 0.026 mol) is added in one portion, and the mixture is stirred at 20-25°C for 8 hr (Note 15). The reaction mixture is poured into water and extracted with three 60-mL portions of dichloromethane. The combined organic extracts are washed with saturated sodium bicarbonate and then with water, and dried over magnesium sulfate. The drying agent is removed by filtration and the solution is evaporated to dryness with a rotary evaporator. The resulting pale yellow solid is column-chromatographed on silica gel (250 g, 60 cm x 4.5 cm column) using dichloromethane eluent (Note 16) to give 950 mg (14%) of estrone 3-methyl ether

starting material and 4.8 g (66%) of 16 α -fluoroestrone 3-methyl ether as a colorless solid, mp 157°C (Notes 17, 18, 19).

2. Notes

1. A cylinder containing 20% fluorine/80% nitrogen was obtained from Air Products & Chemicals, Inc.

2. The checkers used a Matheson model B15F-679 single-stage pressure regulator, a model 63-5512 pressure gauge, and a model 7825 flowmeter. Information on equipment designed to handle fluorine can be found in the bulletin Tech-Brief TB-115, published by Matheson Gas Products.

3. Anhydrous pyridine (99+%) packaged under nitrogen was purchased from Aldrich Chemical Company, Inc., and used without further purification.

4. Sodium trifluoromethanesulfonate (triflate) was prepared from trifluoromethanesulfonic acid (Aldrich Chemical Company, Inc.) as follows: A solution of 26.5 g (0.66 mol) of sodium hydroxide in 50 mL of water was added dropwise to 100 g (0.67 mol) of triflic acid chilled in an ice bath. The solution was concentrated to dryness with a rotary evaporator, and the residual solid was recrystallized from 65 mL of acetonitrile. The collected solid was dried at 80°C under vacuum for 24 hr to give 90 g of pure sodium triflate.

5. Acetonitrile was distilled from calcium hydride under nitrogen immediately before use.

6. A powerful magnetic stirrer was used to obtain a stirring rate of about 80 r.p.s. The checkers also used a VIBRO-Mixer E1 (Chemapec, Inc.). The checkers found that the yield was unaffected if the fluorine is introduced below rather than above the surface of the solution.

7. A substantial excess of fluorine over the theoretical, equimolar amount is needed to complete the reaction because of the low solubility of fluorine. The amount of fluorine required can vary depending upon the scale of reaction, the flow rate, and the efficiency of mixing.

8. The submitters carried out the filtration procedure in air. The procedure in wet air should be avoided.

9. The submitters report obtaining 13.2 g of crude product, mp 181-184°C, and 12.0 g (81%) of recrystallized material, mp 185-187°C.

10. The product obtained by the checkers is pure by NMR analyses. N-Fluoropyridinium triflate (**1**) has the following spectral properties: ^1H NMR (CD_3CN) δ : 8.32 (m, 2 H), 8.77 (m, 1 H), 9.33 (dd, 2 H, $J = 16, 7$); ^{19}F NMR (CD_3CN) δ : 48.8 (bs, 1 F, N-F), -77.6 (s, 3 F, CF_3); IR (Nujol on NaCl plate) cm^{-1} : 3140 (s), 3120 (s), 3080 (s), 3050 (s), 1600 (m), 1485 (s), 1475 (s), 1330 (w), 1270 (s), 1250 (s), 1220 (s), 1200 (s), 1175 (s), 1160 (s), 1090 (m), 1055 (w), 1020 (s), 805 (m), 770 (s), 755 (m), 630 (s).

11. N-Fluoropyridinium triflate is stable and can be stored indefinitely under a dry atmosphere. It slowly decomposes in water. The submitters report that it has a half-life of 13 days in D_2O at room temperature.

12. Estrone 3-methyl ether (3-methoxyestra-1,3,5(10)-trien-17-one) was purchased from Sigma Chemical Company.

13. Trimethylsilyl triflate was obtained from Aldrich Chemical Company, Inc., and used without further purification.

14. The product exhibits the following partial spectral data: ^1H NMR (CDCl_3) δ : 0.21 (s, 9 H, CH_3Si), 0.87 (s, 3 H, 18- CH_3), 3.77 (s, 3 H, OCH_3), 4.53 (m, 1 H, 16-H). This silyl enol ether is sensitive to hydrolysis, and the submitters recommend that it be isolated in the same flask which is used for its subsequent reaction in Part C.

15. Crystals of **1** gradually disappear as the reaction proceeds, and the mixture turns orange and finally becomes homogeneous when the reaction is completed.

16. Each fraction was monitored by thin-layer chromatography on silica gel (Merck Silica Gel 60 F-254). The R_f values (dichloromethane) of the product and starting estrone 3-methyl ether are 0.53 and 0.40, respectively.

17. The product has the following characteristic spectral properties: ^1H NMR (360 MHz, CDCl_3) δ : 0.95 (s, 3 H, 18- CH_3), 3.77 (s, 3 H, OCH_3), 5.13 (dd, 1 H, $J = 50.6$, 7.3, 16 β -H), 6.64 (d, 1 H, $J = 2.7$, 4-H), 6.72 (dd, 1 H, $J = 8.6$, 2.7, 2-H), 7.19 (d, 1 H, $J = 8.6$, 1-H); ^{19}F NMR (CDCl_3) δ : -192.7 (m); IR (KBr) cm^{-1} : 2900, 2850, 1750, 1600, 1500, 1460, 1440, 1310, 1240, 1030, 1000; MS m/e (relative intensity) 304 (2.7), 303 (21.5), 302 (M^+) (100), 301 (3.7).

18. The product contains about 4% of the 16 β -fluoroestrone epimer; ^1H NMR (360 MHz, CDCl_3) δ : 4.76 (dt, $J = 50$, 8; 16 α -H); ^{19}F NMR (CDCl_3) δ : -185.3 (dd, $J = 50$, 22; 16 β -F).

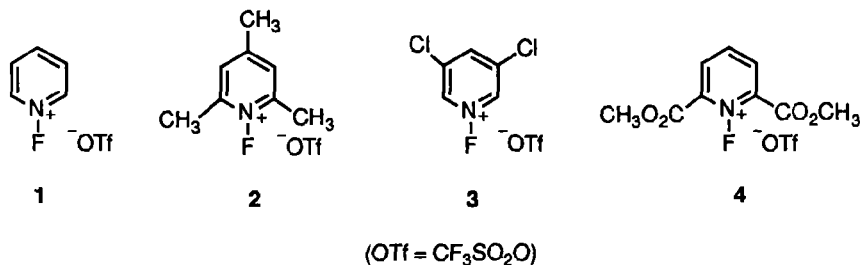
19. Identical yields of recovered starting material and product were obtained when Parts B and C were run on 2.5 times the scale. The submitters report obtaining a 78% yield of product, mp 145-149°C (recrystallized from ethyl acetate/hexane after chromatography) containing a small but unspecified amount of its epimer, along with 11% recovered starting material and 12% 2-pyridyl triflate, which is a decomposition product of **1**. Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{O}_2\text{F}$: C, 75.47; H, 7.66. Found: C, 75.52; H, 7.81.

3. Discussion

Electrophilic fluorinating agents such as F_2 ,³ CF_3OF ,⁴ FCIO_3 ,⁵ CF_3COOF ,⁶ CH_3COOF ,⁷ XeF_2 ,⁸ and CsSO_4F ⁹ require the use of special equipment and techniques because of their explosive, toxic, unstable, or hygroscopic nature. N-Fluoroperfluoropiperidine,¹⁰ N-fluoropyridone,¹¹ and N-fluoro-N-alkyltoluenesulfonamides¹² are easy to handle, but their low reactivity limits the scope of their

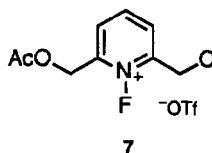
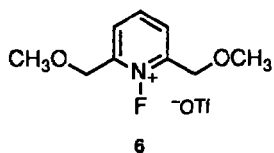
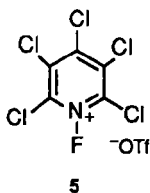
applications. More reactive N-fluoroperfluorosulfonamides¹³ have been recently reported as particularly useful reagents for aromatic fluorination.

N-Fluoropyridinium trifluoromethanesulfonate (triflate) and its derivatives are effective, stable fluorinating agents with varying degrees of fluorinating power.¹⁴ The procedure given here represents a general method for preparing substituted N-fluoropyridinium triflates. Triflates **2-4** can be made in good yields in the same manner as **1**, although instead of sodium triflate, potassium triflate is required for **2**, and lithium triflate for **3** and **4**.



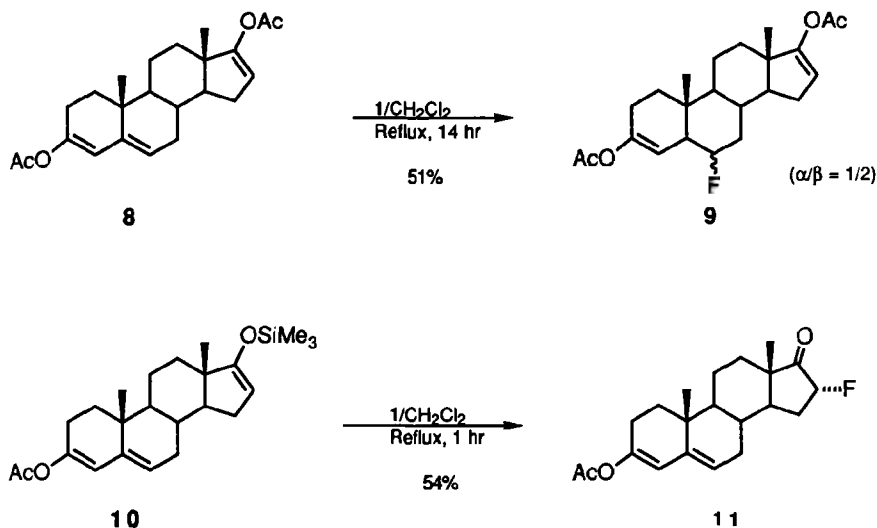
The reactivity of the N-fluoropyridinium salts can be adjusted by varying the substituents on the pyridine ring. Triflates **1-4**, whose fluorinating power increases in the order **2** < **1** < **3** < **4**, are the most generally useful reagents. The most powerful reagent available is **5**;¹⁵ **6** and **7**¹⁶ recently have been developed as mild, efficient reagents. The reagents are all stable, crystalline materials and thus can be handled routinely. Examples of fluorinations which illustrate their use are given in Table I. The weakest reagent **2** is most suited for fluorinating reactive or easily oxidized compounds, such as carbanions, enamines, and sulfides, whereas the more potent reagents **4** and **5** are preferred for fluorinating aromatic rings. Salt **1** of intermediate

reactivity is effective with moderately electron-rich substrates, such as enol alkyl ethers, enol silyl ethers, and activated vinyl acetates.



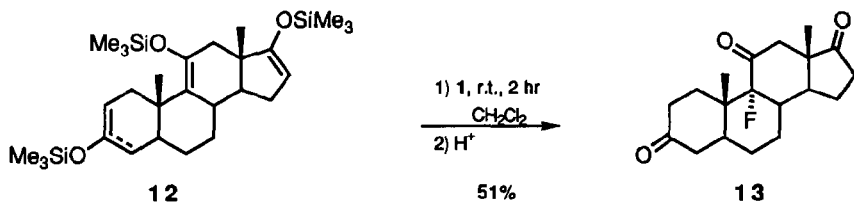
N-Fluoropyridinium triflate shows high regioselectivity in its fluorinations, as evidenced by the results in Schemes 1 and 2. With steroids **8** and **10**, each having two reactive sites, **1** reacts to give exclusively the 6-fluoro steroid **9** and the 16-fluoro steroid **11**, respectively. Thus **1** can distinguish between a conjugated and non-conjugated vinyl acetate, and between an enol silyl ether and a conjugated vinyl acetate in its fluorinations. The present procedure for converting the estrone enol silyl ether to the 16 α -fluoroestrone also shows that **1** selectively reacts with an enol silyl ether moiety in the presence of an activated aromatic ring.

Scheme 1



The fluorination of 12, easily prepared from the corresponding triketo steroid, with an equimolar amount of 1 (Scheme 2) shows the remarkable ability of 1 to distinguish di-substituted from tri-substituted enol silyl ethers. The 9 α -fluoro steroid 13 is produced in 51% yield (78% based on recovered triketo steroid) and the combined yield of the other fluorinated products is only 4.6%.¹⁷ It thus is apparent that 1 reacts almost exclusively with the trisubstituted enol ether moiety. The new, selective direct fluorination at the 9 α -position holds considerable promise as a means to prepare biologically important 9 α -fluoro steroids.¹⁸

Scheme 2



With the increasing importance of organofluorine compounds in the development of new materials, pharmaceuticals, and agricultural chemicals, N-fluoropyridinium salts should find extensive use as mild and selective fluorinating agents.

1. (a) Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan; (b) Onoda Cement Company, Japan. Present address for T.U.: Daikin Industries, Ltd., Chemical Division, 1-1 Nishi Hitotsuya, Settsu-Shi, Osaka 566, Japan.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number): (Registry Number)

N-Fluoropyridinium triflate: Pyridinium, 1-fluoro-, salt with trifluoromethanesulfonic acid (1:1) (12); (107263-95-6)

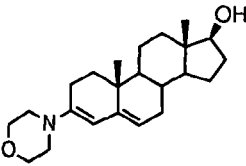
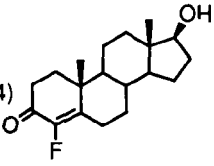
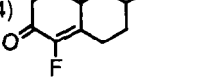
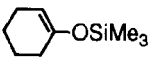
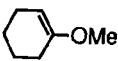
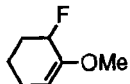
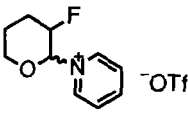
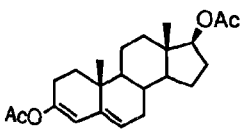
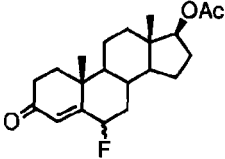
Pyridine (8,9); (110-86-1)

Sodium triflate: Methanesulfonic acid, trifluoro-, sodium salt (8,9); (2926-30-9)

Trifluoromethanesulfonic acid: Methanesulfonic acid, trifluoro- (8,9); (1493-13-6)

Fluorine (8,9); (7782-41-4)

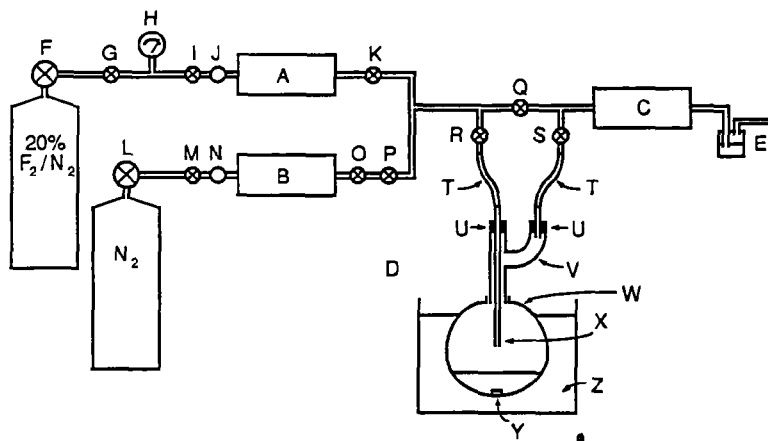
TABLE I
ELECTROPHILIC FLUORINATIONS WITH N-FLUOROPYRIDINIUM TRIFLATES

Substrate	Reagent ^a	Conditions	Product	Yield (%) ^b
$n\text{-C}_{12}\text{H}_{25}\text{MgCl}$	2	0°C, 30 min in Et ₂ O	$n\text{-C}_{12}\text{H}_{25}\text{F}$	75 ^c
$\text{NaCH}(\text{COOEt})_2$	2	0°C, 2 hr in THF	$\text{CHF}(\text{COOEt})_2$ $\text{CF}_2(\text{COOEt})_2$	42 6
$\text{CH}_2(\text{COOEt})_2$	2^d	AlCl_3 , ^e 80°C 24 hr in $\text{CH}_2\text{ClCH}_2\text{Cl}$	$\text{CF}_2(\text{COOEt})_2$ $\text{CHF}(\text{COOEt})_2$	76 ^f 19 ^f
$p\text{-ClC}_6\text{H}_4\text{SCH}_3$	2	R.t., 8 hr in CH_2Cl_2	$p\text{-ClC}_6\text{H}_4\text{SCH}_2\text{F}$	76
	2	1) -15°C, 1 hr in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}(1/4)$		54
	1	2) R.t., ca. 12 hr in c. HCl/DMF		46
	1	R.t., 7 hr in CH_2Cl_2		87 ^c
	1	60°C, 30 min in $\text{CH}_2\text{ClCH}_2\text{Cl}$		63 ^f
	1	Reflux, 7 hr in CH_2Cl_2		86 ^h
	1	Reflux, 10 hr in CH_2Cl_2		71 ⁱ

PhOH	3	Reflux, 5 hr in CH ₂ Cl ₂	F-C ₆ H ₄ OH (o:p)	57 ^c (3.3:1)
PhOMe	3	80°C, 18 hr in CH ₂ ClCH ₂ Cl	F-C ₆ H ₄ OMe (o:p)	64 ^c (1:1)
PhOMe	4	Reflux, 23 hr in CH ₂ Cl ₂	F-C ₆ H ₄ OMe (o:p)	65 ^c (1:1)
PhNHCOOEt	3	80°C, 5 hr in CH ₂ ClCH ₂ Cl	F-C ₆ H ₄ NHCOOEt (o:p)	54 (2.2:1)

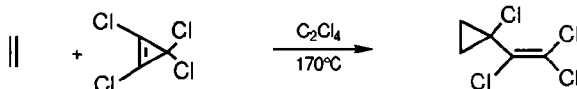
a) Equimolar N-fluoropyridinium triflate unless noted otherwise. b) Isolated yields unless noted otherwise. c) GLPC yields. d) 2 Equivalents of **2**. e) 0.4 Equivalents of AlCl₃. f) ¹⁹F NMR yields. g) 1.5 Equivalents of dihydropyran. h) cis/trans = 1/1. i) α/β = 1/2.

Figure 1



A: Flowmeter (Matheson model 7825); B: Flowmeter (Hastings model CST); C: Alumina trap; D: Reactor system; E: Bubble counter containing perfluorotributylamine; F: Pressure regulator (Matheson model 63-5512); G, I, K, O, P: Stainless steel valves; H: Pressure gauge (Matheson model 63-5512); J, N: Stainless steel filters; L: Pressure regulator for nitrogen; M, Q, R, S: Brass valves; T: Viton tubing; U: Teflon corks; V: Pyrex Claisen adaptor; W: Pyrex flask; X: Pyrex tube; Y: Teflon-coated stirring bar; Z: -40°C Cooling bath.

1-CHLORO-1-(TRICHLOROETHENYL)CYCLOPROPANE
(Cyclopropane, 1-chloro-1-(trichloroethenyl)-)



Submitted by Thomas Liese, Frank Jaekel, and Armin de Meijere.¹

Checked by John R. Berry, James S. Piecara, and Bruce E. Smart.

1. Procedure

A 1-L Hastelloy C-276 shaker tube (Note 1) fitted with a temperature sensor, rupture-disk safety device, and a gas-inlet valve attached to an ethylene cylinder is charged with 120.0 g (0.675 mol) of freshly distilled tetrachlorocyclopropene (Note 2), 350 mL of dry tetrachloroethylene (Note 3), and 10 g of anhydrous sodium carbonate (Note 4). The tube is pressurized to 20 atm with ethylene and shaken for 3 hr. The ethylene cylinder is disconnected, the pressure vessel is gradually heated to 170°C over a 30-min period, and it is shaken at this temperature for 19.5 hr. The vessel is allowed to cool to room temperature, and the excess ethylene is slowly released and bubbled through a wash bottle containing methylene chloride (Note 5). The light brown liquid in the shaker tube is decanted and the remaining solid washed twice with 50 mL of methylene chloride. The organic phases are combined and the methylene chloride is removed by distillation. The residual liquid is distilled at water-aspirator vacuum through a 40-cm Vigreux column. The solvent tetrachloroethylene, bp 35°C (27 mm), is collected (Note 6), followed by 104.1-105.6 g (75-76%) of 1-chloro-1-(trichloroethenyl)cyclopropane as a colorless liquid, bp 81-83°C (27 mm) (Note 7).

2. Notes

1. The submitters used a 1-L autoclave lined with Hastelloy C-4. Hastelloy C materials are high nickel alloys. A highly resistant alloy is employed to avoid possible side reactions.

2. Tetrachlorocyclopropene was prepared from sodium trichloroacetate and trichloroethylene.^{2,3} It is also available from the Aldrich Chemical Company, Inc., Eastman Organic Chemicals, and the Merck-Schuchardt Company (in Europe).

3. Tetrachloroethylene was obtained from the Aldrich Chemical Company, Inc. and distilled from phosphorus pentoxide prior to use.

4. Anhydrous sodium carbonate was obtained from the J. T. Baker Chemical Company and dried under vacuum at 130°C.

5. The wash bottle serves to trap any product carried with the ethylene vapors, to monitor and control the release of ethylene pressure and to indicate when no excess pressure remains, and to diminish the release of toxic materials.

6. The receiver was cooled in an ice bath to avoid loss of the tetrachloroethylene distillate.

7. The submitters obtained 111-116 g of product, bp 72-75°C (14-18 mm). The spectral properties of 1-chloro-1-(trichloroethenyl)cyclopropane are as follows; IR (neat) cm^{-1} : 3100 (CH), 3020 (CH), 1585 (C=C), 1415, 1170, 1040, 1015, 940, 910, 875, 800, 750, 645; ^1H NMR (CDCl_3) δ : 1.42 (m, 2 H), 1.52 (m, 2 H).

3. Discussion

Tetrachlorocyclopropene has been known for some time to be a reasonably reactive dienophile.⁴ Its thermal ring opening to perchlorovinyl carbene is in accord with the behavior of other cyclopropenes under thermolytic conditions,⁵ but the

efficiency with which this vinyl carbene intermolecularly adds to a wide variety of olefins^{6,7} is unprecedented. The resulting 1-chloro-1-(trichloroethenyl)cyclopropanes^{6,7} can be reductively dechlorinated to vinylcyclopropanes,⁶ transformed into variously-substituted cyclopropylacetylenes^{7,8} or cyclopropylidenacetates.⁹ The simple cyclopropyl derivatives, accessible from the reported 1-chloro-1-(trichloroethenyl)cyclopropane, like methyl 2-chloro-2-cyclopropylidenacetate (see accompanying procedure) and 1-trimethylsilyl-1-(trimethylsilylethynyl)cyclopropane (prepared by reductive silylation with magnesium/chlorotrimethylsilane in tetrahydrofuran¹⁰), are especially useful building blocks for the construction of complex organic molecules.^{11,12,13}

1. Institut für Organische Chemie der Universität Hamburg, Martin-Luther-King-Platz 6, D-2000 Hamburg 13, Federal Republic of Germany. Present address: Institut für Organische Chemie der Georg-August-Universität, Tammannstrasse 2, D-3400 Göttingen, Federal Republic of Germany.
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Appendix

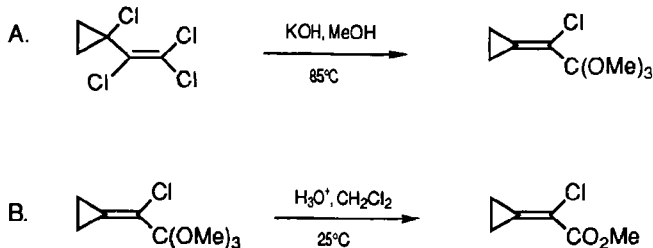
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-Chloro-1-(trichloroethenyl)cyclopropane: Cyclopropane, 1-chloro-1-(trichloroethenyl)- (11); (82979-27-9)

Tetrachlorocyclopropene: Cyclopropene, tetrachloro- (8,9); (6262-42-6)

METHYL 2-CHLORO-2-CYCLOPROPYLIDENACETATE

(Acetic acid, chlorocyclopropylidene-, methyl ester)



Submitted by Thomas Liese, Fereydoun Seyed-Mahdavi, and Armin de Meijere.¹

Checked by James S. Piecara and Bruce E. Smart.

1. Procedure

A. *Trimethyl 2-chloro-2-cyclopropylidenethanoate*. A 1-L, two-necked, round-bottomed flask equipped with a mechanical stirrer and a reflux condenser is charged with 40.0 g (0.19 mol) of 1-chloro-1-(trichloroethenyl)cyclopropane (Note 1), 120 g of potassium hydroxide, and 300 mL of methanol (Note 2). The mixture is stirred for 16-18 hr in an oil bath at 85°C. After the solution is cooled to room temperature, it is diluted with 1 L of ice water. The mixture is then transferred to a 3-L separatory funnel and extracted with three 200-mL portions of ether. The combined ether phases are washed with three 150-mL portions of saturated brine, dried over anhydrous magnesium sulfate, and filtered. The solvent is removed from the filtrate by distillation at atmospheric pressure, and the residue is distilled through a short-path column under water-aspirator vacuum to give 14.5-15.4 g (39-41%) of trimethyl 2-chloro-2-cyclopropylidenethanoate, bp 103-105°C (20 mm) (Notes 3 and 4).

B. Methyl 2-chloro-2-cyclopropylidenacetate. A 250-mL, one-necked, round-bottomed flask is charged with 60 mL of methylene chloride (Note 2), 3.5 g of a strongly acidic ion-exchange resin (Note 5), and 11.0 g (0.057 mol) of trimethyl 2-chloro-2-cyclopropylidenorthoacetate. The mixture is stirred for 12 hr at room temperature. The ion-exchange resin is removed by filtration and washed with three 10-mL portions of methylene chloride. The combined organic solutions are dried over anhydrous magnesium sulfate, filtered, and distilled at atmospheric pressure to remove the solvent. The residue is distilled through a short-path column under reduced pressure to give 6.2-6.7 g (74-80%) of methyl 2-chloro-2-cyclopropylidenacetate, bp 95-97°C (10 mm) (Notes 6, 7, and 8).

2. Notes

1. 1-Chloro-1-(trichloroethenyl)cyclopropane was prepared from tetrachlorocyclopropene as described in the accompanying procedure, p. 144.

2. Methanol and methylene chloride were obtained from E. M. Science (Merck & Company, Inc.) and used without further purification.

3. The checkers obtained the same yields for 0.10-mol scale runs. The submitters report yields of 54-58%, however.

4. The submitters report bp 107-109°C (20 mm). The spectral properties of 2-chloro-2-cyclopropylidenorthoacetate are as follows: IR (neat) cm^{-1} : 2840 (OCH_3), 1780 ($\text{C}=\text{C}$); ^1H NMR (CDCl_3) δ : 1.27-1.80 (m, 4 H), 3.23 (s, 9 H).

5. The checkers used analytical grade AG 50W-X8 resin, which is a strongly acidic polystyrene gel type resin, supplied by Bio-Rad Laboratories. The submitters used the large-pore, strongly acidic ion-exchange resin Lewatit SPC 118, supplied by Bayer AG.

6. The submitters report obtaining 7.0-7.5 g (84-90%) of product, bp 60-63°C (3.7 mm), and note that 4.7-5.0 g of analytically pure material, mp 33-34°C, can be obtained by crystallization at -20°C from 10-15 mL of pentane and the remaining 2.3-2.5 g of product can be recovered from the mother liquor by chromatography on silica gel (60 g) using a 5:1 mixture of pentane/diethyl ether as the eluent.

7. The product obtained by the checkers is pure by NMR analysis and it shows the following spectral properties: IR (neat) cm^{-1} : 3080 (cyclopropyl CH), 1720 (C=O); ^1H NMR (CDCl_3) δ : 1.42-1.52 (m, 2 H), 1.69-1.78 (m, 2 H), 3.84 (s, 3 H).

8. The submitters report that the product can be obtained in higher yields without isolation of the intermediate orthoester according to the following procedure: To a solution of sodium methoxide, freshly prepared by dissolving 14.0 g (0.61 mol) of sodium metal in 200 mL of dry methanol, at 65°C is added with stirring 30.0 g of 1-chloro-1-(trichloroethenyl)cyclopropane. The stirred mixture is refluxed (oil bath temperature of 110°C) for 72 hr. After the solution is cooled to room temperature, 200 mL of ice water is added and the mixture is extracted with three 200-mL portions of ether. The combined ether extracts are washed with three 50-mL portions of saturated brine, dried over anhydrous magnesium sulfate, and filtered. The solvent is removed from the filtrate by distillation at atmospheric pressure. The residue is dissolved in 100 mL of methylene chloride, 10 g of a strongly acidic ion-exchange resin is added (Note 5), and the mixture is stirred at room temperature for 48 hr. The resin is removed by filtration and is washed with three 10-mL portions of methylene chloride. The combined organic solutions are dried over anhydrous magnesium sulfate, filtered, and the solvent is removed from the filtrate by distillation at atmospheric pressure. The residual oil is taken up in 200 mL of pentane and the solution is refrigerated at 5°C. The precipitated crystals are collected by filtration to yield 11-13 g (51-60%) of 2-chloro-2-cyclopropylidenacetate. The checkers obtained a 50% yield of pure product, mp 40-41°C, when this procedure was repeated on about half the scale.

3. Discussion

This procedure is applicable to a number of substituted 1-chloro-1-(trichloroethenyl)cyclopropanes,² and in general gives good yields of methyl 2-chloro-2-cyclopropylidenacetates.³ These are highly reactive Michael acceptors which rapidly react with nucleophiles to give 1'-substituted-2-chloro-2-cyclopropylacetates. The parent 2-chloro-2-cyclopropylidenacetate is a particularly useful building block in organic synthesis since it adds to cyclic dienolates to give complex skeletons in high yields.^{4,5} In addition, it is a reactive dienophile^{5,6} and can be further modified to 2-arylthio-substituted derivatives as well as to the parent methyl 2-cyclopropylidenacetate in high yields.⁷ The corresponding ethyl 2-cyclopropylidenacetate has been prepared in poor yield by a Wittig-Horner-Emmons olefination of cyclopropanone hemiacetal magnesium salt (8%),⁸ and more recently in vastly improved yield (87%) by the benzoic acid-catalyzed Wittig olefination.⁹

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

Methyl 2-chloro-2-cyclopropylidenacetate: Acetic acid, chlorocyclopropylidene methyl ester (11); (82979-45-1)

Trimethyl 2-chloro-2-cyclopropylidenorthoacetate: Cyclopropane, (1-chloro-2,2,2-trimethoxyethylidene)- (11); (82979-34-8)

1-Chloro-1-(trichloroethenyl)cyclopropane: Cyclopropane, 1-chloro-1-(trichloroethenyl)- (11); (82979-27-9)

SYNTHESIS OF (-)-D-2,10-CAMPHORSULTAM
(3H-3a,6-Methano-2,1-benzisothiazole, 4,5,6,7-tetrahydro-
8,8-dimethyl-2,2-dioxide, (3aS)-)



Submitted by Michael C. Weismiller, James C. Towson, and Franklin A. Davis.¹

Checked by David I. Magee and Robert K. Boeckman, Jr.

1. Procedure

(-)-2,10-Camphorsultam. A dry, 2-L, three-necked, round-bottomed flask is equipped with a 1.5-in egg-shaped Teflon stirring bar, a 250-mL addition funnel, and a 300-mL Soxhlet extraction apparatus equipped with a mineral oil bubbler connected to an inert gas source. The flask is charged with 600 mL of dry tetrahydrofuran (THF) (Note 1) and 6.2 g (0.16 mol) of lithium aluminum hydride (Note 2). Into the 50-mL Soxhlet extraction thimble is placed 35.0 g (0.16 mol) of (-)-(camphorsulfonyl)imine (Note 3) and the reaction mixture is stirred and heated at reflux. After all of the (camphorsulfonyl)imine has been siphoned into the reaction flask (3-4 hr), the mixture is allowed to cool to room temperature. The unreacted lithium aluminum hydride is cautiously hydrolyzed by dropwise addition of 200 mL of 1 N hydrochloric acid via the addition funnel (Note 4). After the hydrolysis is complete the contents of the flask are transferred to a 1-L separatory funnel, the lower, silver-colored aqueous layer is separated, and the upper layer placed in a 1-L Erlenmeyer flask. The aqueous phase

is returned to the separatory funnel and washed with methylene chloride (3 x 100 mL). After the reaction flask is rinsed with methylene chloride (50 mL), the organic washings are combined with the THF phase and dried over anhydrous magnesium sulfate for 10-15 min. Filtration through a 300-mL sintered glass funnel of coarse porosity into a 1-L round-bottomed flask followed by removal of the solvent on a rotary evaporator gives 33.5 g (95%) of the crude (-)-2,10-camphorsultam. The crude sultam is placed in a 250-mL Erlenmeyer flask and crystallized from approximately 60 mL of absolute ethanol. The product is collected on a 150-mL sintered glass funnel of coarse porosity and dried in a vacuum desiccator to give 31.1 g (88%) of the pure sultam. A second crop of crystals can be gained by evaporating approximately half the filtrate; the residue is crystallized as above to give 1.4 g (4%). The combined yield of white crystalline solid, mp 183-184°C, $[\alpha]_D -30.7^\circ$ (CHCl₃, c 2.3) is 92% (Notes 5, 6).

2. Notes

1. Tetrahydrofuran (Aldrich Chemical Company, Inc.) was distilled from sodium benzophenone.
2. Lithium aluminum hydride was purchased from Aldrich Chemical Company, Inc.
3. (-)-(Camphorsulfonyl)imine, [(7S)-(-)-10,10-dimethyl-5-thia-4-azatricyclo-[5.2.1.0^{3,7}]dec-3-ene 5,5-dioxide] was prepared by the procedure of Towson, Weismiller, Lal, Sheppard, and Davis, *Organic Syntheses*, **1990**, 69, 158.
4. The addition must be very slow at first (1 drop/5 sec) until the vigorous reaction has subsided.

5. The NMR spectrum of (-)-2,10-camphorsultam is as follows: ^1H NMR (CDCl_3) δ : 0.94 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 1.33 (m, 1 H), 1.47 (m, 1 H), 1.80-2.05 (5 H), 3.09 (d, 1 H, $J = 14$), 3.14 (d, 1 H, $J = 14$), 3.43 (m, 1 H), 4.05 (br s, 1 H, NH); ^{13}C NMR (CDCl_3) δ : 20.17 (q, CH_3), 26.51 (t), 31.55 (t), 35.72 (t), 44.44 (d), 47.15 (s), 50.08 (t), 54.46 (s), 62.48 (d).

6. Checkers obtained material having the same mp (183-184°C) and $[\alpha]_D -31.8^\circ$ (CHCl_3 , c 2.3).

3. Discussion

(-)-2,10-Camphorsultam was first prepared by the catalytic hydrogenation of (-)-(camphorsulfonyl)imine over Raney nickel.² Lithium aluminum hydride reduction was used by Oppolzer and co-workers in their synthesis of the sultam.^{3,4} However, because of the low solubility of the sultam in tetrahydrofuran, a large amount of solvent was required.⁴ In the procedure described here the amount of solvent is significantly reduced by using a Soxhlet extractor to convey the imine slowly into the reducing medium.⁵

Oppolzer's chiral auxiliary,⁶ (-)-2,10-camphorsultam, is useful in the asymmetric Diels-Alder reaction,^{3,4} and for the preparation of enantiomerically pure β -substituted carboxylic acids⁷ and diols,⁸ in the stereoselective synthesis of Δ^2 -isoxazolines,⁹ and in the preparation of N-fluoro (-)-2,10-camphorsultam, an enantioselective fluorinating reagent.¹⁰

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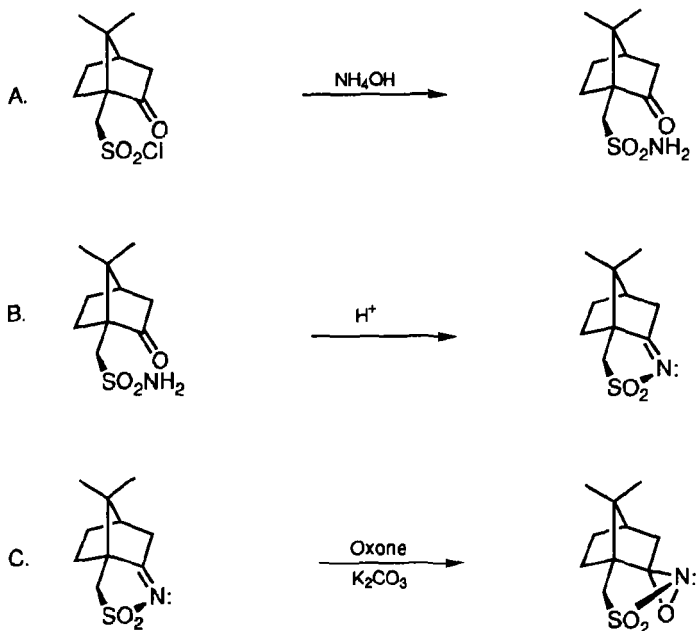
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(-)-(Camphorsulfonyl)imine: 3H-3a,6-Methano-2,1-benzisothiazole, 4,5,6,7-tetrahydro-8,8-dimethyl-, 2,2-dioxide, (3aS)- (9); (60886-80-8)

(-)-D-2,10-Camphorsultam: 3H-3a,6-Methano-2,1-benzisothiazole, hexahydro-8,8-dimethyl-, 2,2-dioxide, [3aS-(3a α ,6 α ,7a β)]- (11); (94594-90-8)

**SYNTHESIS OF (+)-(2R,8aS)-10-(CAMPHORYLSULFONYL)OXAZIRIDINE
(4H-4a,7-Methanooxazirino[3,2-l][2,1]benziso-thiazole,
tetrahydro-9,9-dimethyl-, 3,3-dioxide, [4aS-(4a α ,7 α ,8aR *)])**



Submitted by James C. Towson, Michael C. Weismiller, G. Sankar Lal,

Aurelia C. Sheppard, and Franklin A. Davis.¹

Checked by David I. Magee and Robert K. Boeckman, Jr.

1. Procedure

A. *(+)-(1S)-10-Camphorsulfonamide*. Into a 2-L, three-necked, round-bottomed flask equipped with mechanical stirrer, 65-mm Teflon stirring blade, and a 250-mL

dropping funnel is placed 450 mL of reagent grade ammonium hydroxide. The reaction mixture is cooled to 0°C in an ice bath and stirred vigorously. A solution of 50.0 g (0.2 mol) of (+)-10-camphorsulfonyl chloride (Note 1) in 450 mL of methylene chloride is then added dropwise in two portions over 30 min. The reaction mixture is stirred for an additional 2 hr at this temperature, transferred to a 1000-mL separatory funnel and the phases are separated. The aqueous phase is washed with methylene chloride (2 x 100 mL) and the combined organic extracts are dried for 10-15 min over anhydrous magnesium sulfate. Filtration and removal of the solvent using a rotary evaporator gives 41.5 g (90%), mp 125-128°C, of the crude sulfonamide (Notes 2 and 3).

B. (-)-(Camphorsulfonyl)imine. A 1-L, round-bottomed flask is equipped with a two-inch egg-shaped magnetic stirring bar, a Dean-Stark water separator, and a double-walled condenser containing a mineral oil bubbler connected to an inert gas source. Into the flask are placed 5 g of Amberyl 15 ion exchange resin (Note 4) and 41.5 g of the crude (+)-(1S)-camphorsulfonamide in 500 mL of toluene. The reaction mixture is heated at reflux for 4 hr. After the reaction flask is cooled, but while it is still warm (40-50°C), 200 mL of methylene chloride is slowly added to dissolve any (camphorsulfonyl)imine that crystallizes. The solution is filtered through a 150-mL sintered glass funnel of coarse porosity and the reaction flask and filter funnel are washed with an additional 75 mL of methylene chloride.

Isolation of the (-)-(camphorsulfonyl)imine is accomplished by removal of the toluene on the rotary evaporator. The resulting solid is recrystallized from absolute ethanol (750 mL) to give white crystals, 34.5-36.4 g (90-95%), mp 225-228°C; $[\alpha]_D^{25}$ -32.7° (CHCl₃, c 1.9) (Note 5).

C. (+)-(2R,8aS)-10-(Camphorylsulfonyl)oxaziridine. A 5-L, three-necked, round-bottomed Morton flask is equipped with an efficient mechanical stirrer, a 125-mm Teflon stirring blade, a Safe Lab stirring bearing (Note 6), and a 500-mL addition

funnel. Into the flask are placed the toluene solution of (-)-(camphorsulfonyl)imine (39.9 g, 0.187 mol) prepared in Step B and a room temperature solution of 543 g (3.93 mol, 7 equiv based on oxone) of anhydrous potassium carbonate dissolved in 750 mL of water. The reaction mixture is stirred vigorously and a solution of 345 g (0.56 mol, 6 equiv of KHSO_5) of oxone dissolved in 1250 mL of water is added dropwise in three portions over 45 min (Notes 7 and 8). Completion of the oxidation is determined by TLC (Note 9) and the reaction mixture is filtered through a 150-mL sintered glass funnel of coarse porosity to remove solids. The filtrate is transferred to a 3-L separatory funnel, the toluene phase is separated and the aqueous phase is washed with methylene chloride (3 x 100 mL). The filtered solids and any solids remaining in the Morton flask are washed with an additional 200 mL of methylene chloride. The organic extracts are combined and washed with 100 mL of saturated sodium sulfite, dried over anhydrous magnesium sulfate for 15-20 min, filtered and concentrated on the rotary evaporator. The resulting white solid is crystallized from approximately 500 mL of hot 2-propanol to afford, after drying under vacuum in a desiccator, 35.9 g (84%) of white needles, mp 165-167°C, $[\alpha]_D +44.6^\circ$ (CHCl_3 , c 2.2) (Notes 10, 11).

(-)-(2S,8aR)-10-(Camphorylsulfonyl)oxaziridine is prepared in a similar manner starting from (-)-10-camphorsulfonyl chloride; mp 166-167°C, $[\alpha]_D -43.6^\circ$ (CHCl_3 , c 2.2).

2. Notes

1. (-)-10-Camphorsulfonyl chloride was prepared from 50 g of (1S)-(+)-10-camphorsulfonic acid purchased from Aldrich Chemical Company, Inc. using the procedure described by Bartlett and Knox, *Org. Synth., Coll., Vol. V* 1973, 196. Material that was collected on the suction filter and air dried by maintaining suction for 15-20 min was of sufficient purity for the next step. The checkers obtained comparable

or better overall yields of sulfonamide (96%) without isolation of the acid chloride based on (+)-camphoric acid using thionyl chloride to convert the acid to the acid chloride.

2. The crude sulfonamide is contaminated with 5-10% of the (camphorsulfonyl)imine the yield of which increases on standing.

3. The ^1H NMR spectrum of (+)-(1S)-10-camphorsulfonamide is as follows: (CDCl_3) δ : 0.93 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 1.40-2.50 (m, 7 H), 3.14 and 3.53 (ab quartet, 2 H, $\text{CH}_2\text{-SO}_2$, $J = 15.1$), 5.54 (br s, 2 H, NH_2).

4. Amberlyst 15 ion-exchange resin is a strongly acidic, macroreticular resin purchased from Aldrich Chemical Company, Inc.

5. The spectral properties of (-)-(camphorsulfonyl)imine are as follows: ^1H NMR (CDCl_3) δ : 1.03 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.45-2.18 (m, 6 H), 2.65 (m, 1 H), 3.10 and 3.28 (AB quartet, 2 H, $\text{CH}_2\text{-SO}_2$, $J = 14.0$); ^{13}C NMR (CDCl_3) δ : 19.01 (q, CH_3), 19.45 (q, CH_3), 26.64 (t), 28.44 (t), 35.92 (t), 44.64 (d), 48.00 (s), 49.46 (t), 64.52 (s), 195.52 (s); IR (CHCl_3) cm^{-1} : 3030, 2967, 1366. Checkers obtained material having identical melting point and $[\alpha]_D -32.3^\circ$ (CHCl_3 , c 1.8).

6. The SafeLab Teflon bearing can be purchased from Aldrich Chemical Company, Inc. A glass stirring bearing lubricated with silicone grease is unsatisfactory because the dissolved salts solidify in the shaft causing freezing.

7. Efficient stirring is important and indicated by a milky white appearance of the solution.

8. Occasionally batches of oxone purchased from Aldrich Chemical Company, Inc., have exhibited reduced reactivity in this oxidation. Oxone exposed to moisture prior to use also gives reduced reactivity in this oxidation. If this occurs oxone is added until oxidation is complete as determined by TLC (Note 9). Potassium carbonate is added as needed to maintain the pH at approximately 9.0. Oxone stored

in the refrigerator under an inert atmosphere has shown no loss in reactivity for up to six months.

9. Oxidation is generally complete after addition of the oxone solution. The oxidation is monitored by TLC as follows: remove approximately 0.5 mL of the toluene solution from the nonstirring solution, spot a 250-micron TLC silica gel plate, elute with methylene chloride and develop with 10% molybdophosphoric acid in ethanol and heating: (camphorsulfonyl)imine $R_f = 0.28$ and (camphorylsulfonyl)oxaziridine $R_f = 0.62$. If (camphorsulfonyl)imine is detected, stirring is continued at room temperature until the reaction is complete (See Note 8).

If the reaction mixture takes on a brownish color after addition of oxone and has not gone to completion after 30 min, the reaction mixture is filtered through a 150-mL sintered glass funnel of coarse porosity, and the solids are washed with 50 mL of methylene chloride. The aqueous/organic extracts are returned to the 5-L Morton flask, stirred vigorously and 52 g (0.08 mol, 1 equiv KHSO_5) of oxone is added over 5 min and stirring continued until oxidation is complete (approximately 10-15 min).

10. The submitters employed a toluene solution of crude imine prepared in part B and obtained somewhat higher yields (90-95%). However, the checkers obtained yields in this range on one half the scale using isolated sulfonylimine.

11. The spectral properties of (+)-(camphorsulfonyl)oxaziridine are as follows: ^1H NMR (CDCl_3) δ : 1.03 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.45-2.18 (m, 6 H), 2.65 (d, 1 H), 3.10 and 3.28 (AB quartet, 2 H, $\text{CH}_2\text{-SO}_2$, $J = 14.0$); ^{13}C NMR (CDCl_3) δ : 19.45 (q, CH_3), 20.42 (q, CH_3), 26.55 (t), 28.39 (t), 33.64 (t), 45.78 (d), 48.16 (s), 48.32 (t), 54.07 (s), 98.76 (s). The checkers obtained material (mp 165-167°C) having $[\alpha]_D^{+44.7^\circ}$ (CHCl_3 , c 2.2).

3. Discussion

(Camphorsulfonyl)imine has been reported as a by-product of reactions involving the camphorsulfonamide.²⁻⁵ Reychler in 1898 isolated two isomeric camphorsulfonamides,² one of which was shown to be the (camphorsulfonyl)imine by Armstrong and Lowry in 1902.³ Vandewalle, Van der Eycken, Oppolzer and Vullioud described the preparation of (camphorsulfonyl)imine in 74% overall yield from 0.42 mol of the camphorsulfonyl chloride.⁶ The advantage of the procedure described here is that, by using ammonium hydroxide, the camphorsulfonyl chloride is converted to the sulfonamide in >95% yield.⁷ The sulfonamide is of sufficient purity that it can be used directly in the cyclization step, which, under acidic conditions is quantitative in less than 4 hr. These modifications result in production of the (camphorsulfonyl)imine in 86% overall yield from the sulfonyl chloride.

In addition to the synthesis of enantiomerically pure (camphorylsulfonyl)oxaziridine⁷ and its derivatives,⁸ the (camphorsulfonyl)imine has been used in the preparation of (-)-2,10-camphorsultam (Oppolzers' auxiliary),^{6,9} (+)-(3-oxocamphorylsulfonyl)oxaziridine¹⁰ and the N-fluoro-2,10-camphorsultam, an enantioselective fluorinating reagent.¹¹

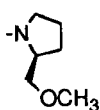
The N-sulfonyloxaziridines are an important class of selective, aprotic oxidizing reagents.¹² Enantiomerically pure N-sulfonyloxaziridines have been used in the asymmetric oxidation of sulfides to sulfoxides (30-91% ee),¹³ selenides to selenoxides (8-9% ee),¹⁴ disulfides to thiosulfinates (2-13% ee),⁵ and in the asymmetric epoxidation of alkenes (19-65% ee).^{15,16} Oxidation of optically active sulfonimines ($R^*SO_2N=CHAr$) affords mixtures of N-sulfonyloxaziridine diastereoisomers requiring separation by crystallization and/or chromatography.¹³

(+)-(Camphorylsulfonyl)oxaziridine described here is prepared in four steps from inexpensive (1S)-(+)- or (1R)-(+)-10-camphorsulfonic acid in 77% overall yield.⁷

Separation of the oxaziridine diastereoisomers is not required because oxidation is sterically blocked from the exo face of the C-N double bond in the (camphorsulfonyl)imine. In general (camphorsulfonyl)oxaziridine exhibits reduced reactivity compared to other N-sulfonyloxaziridines. For example, while sulfides are asymmetrically oxidized to sulfoxides (3-77% ee) this oxaziridine does not react with amines or alkenes.⁷ However, this oxaziridine is the reagent of choice for the hydroxylation of lithium and Grignard reagents to give alcohols and phenols because yields are good to excellent and side reactions are minimized.¹⁷ This reagent has also been used for the stereoselective oxidation of vinylolithiums to enolates.¹⁸

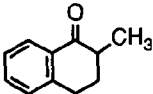
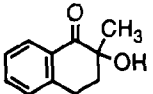
The most important synthetic application of the (camphorylsulfonyl)oxaziridines is the asymmetric oxidation of enolates to optically active α -hydroxy carbonyl compounds.^{12c,19-22} Chiral, nonracemic α -hydroxy carbonyl compounds have been used extensively in asymmetric synthesis, for example, as chiral synthons, chiral auxiliaries, and chiral ligands. This structural array is also featured in many biologically active natural products. This oxidizing reagent gives uniformly high chemical yields regardless of the counterion and stereoselectivities are good to excellent (50-95% ee).¹⁹⁻²² Since the configuration of the oxaziridine three-membered ring controls the stereochemistry, both α -hydroxy carbonyl optical isomers are readily available. Representative examples of the asymmetric oxidation of prochiral enolates by (+)-(2R,8aS)-camphorylsulfonyl)oxaziridine are given in Tables I and II.

TABLE I
ASYMMETRIC OXIDATION OF LITHIUM ENOLATES OF ESTERS AND AMIDES
USING (+)-(2R,8aS)-10-(CAMPHORYLSULFONYL)OXAZIRIDINE

Entry	RC(R')=C(OLi)X			Cosolvent	Temp. (°C)	Product		
	R	R'	X			%Yield ^a	%ee (Config.)	Ref.
1	Ph	H	OCMe ₃	----	-90	82	71 (R)	19
2	PhCH ₂	H	OMe	----	-90	73	58 (R)	19
				HMPA	-90	63	85 (R)	
3	Ph	Me	OMe	----	-78	61	45 (R)	19
4	Ph	H	NC ₄ H ₈	----	-78	70	30 (S)	19
				HMPA	-78	74	50 (R)	
5	Ph	Me	NC ₄ H ₈	----	-78	40	35 (S)	19
				HMPA	-78	35	20 (R)	
								
6	Ph	Me		----	-78	53	48 (S)	21
7				HMPA	-78	65	89 (S)	

^aIsolated yields.

TABLE II
ASYMMETRIC OXIDATION OF KETONE-DERIVED ENOLATES USING (+)-(2R,8aS)-
10-(CAMPHORYLSULFONYL)OXAZIRIDINE

Entry	Ketone	Base/ Cosolvent	Temp. (°C)	α-Hydroxy Ketone		
				%Yield ^a	%ee (Config.)	Ref.
1	PhC(O)CH ₂ Ph	LDA	0	70	68 (S)	20
2		LDA/HMPA	0	64	6 (S)	
3		NHMDS ^b	-78	84	95 (S)	
4	PhC(O)CH ₂ Me	LDA	0	51	43 (S)	20
5		NHMDS	-78	73	62 (S)	
6	Me ₃ CC(O)CH ₂ Me	LDA	0	55	32 (R)	23
7		NHMDS	-78	71	89 (R)	
8	PhCH ₂ C(O)Me	NHMDS	-78	70	40 (S)	23
9		NHMDS/HMPA	-78	76	76 (R)	23
						
10		LDA	0	75	30 (R)	23
11		NHMDS	0	80	16 (R)	23

^aIsolated yields. ^bBis(trimethylsilyl)amide.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(+)-(2R,8aS)-10-(Camphorylsulfonyl)oxaziridine: 4H-4a,7-Methanooxazirino-[3,2-i][2,1]benzisothiazole, tetrahydro-9,9-dimethyl-3,3-dioxide, [4aS-(4a α ,7 α ,8aR*)]-(11); (104322-63-6)

(+)-(1S)-10-Camphorsulfonamide: Bicyclo[2.2.1]heptane-1-methanesulfonamide, 7,7-dimethyl-2-oxo- (1S)- (9); (60933-63-3)

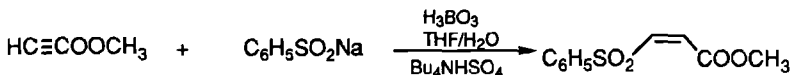
(+)-10-Camphorsulfonyl chloride: Bicyclo[2.2.1]heptane-1-methanesulfonyl chloride, 7,7-dimethyl-2-oxo-, (+)- (9); (21286-54-4)

(1S)-(+)-10-Camphorsulfonic acid: Bicyclo[2.2.1]heptane-1-methanesulfonic acid, 7,7-dimethyl-2-oxo-, (1S)- (9); (3144-16-9)

(-)-(Camphorsulfonyl)imine: 3H-3a,6-Methano-2,1-benzisothiazole, 4,5,6,7-tetrahydro-8,8-dimethyl-, 2,2-dioxide, (3aS)- (9); (60886-80-8)

Oxone: Peroxymonosulfuric acid, monopotassium salt, mixt. with dipotassium sulfate and potassium hydrogen sulfate (9); (37222-66-5)

METHYL (Z)-3-(BENZENESULFONYL)PROP-2-ENOATE
(2-Propenoic acid, 3-(phenylsulfonyl)-, methyl ester, (Z)-)



Submitted by G. C. Hirst¹ and P. J. Parsons.

Checked by Annette Pörlle and Ekkehard Winterfeldt.

1. Procedure

Caution! Methyl propiolate is a lachrymator and must be handled in a fume hood.

A two-phase mixture of methyl propiolate (5.0 g, 59.5 mmol), boric acid (5.5 g, 89 mmol), sodium benzenesulfinate (9.75 g, 59.5 mmol), and tetra-n-butylammonium hydrogen sulfate (3.0 g, 8.75 mmol) (Note 1) in tetrahydrofuran:water (200 mL, 1:1) is stirred vigorously at room temperature for 48 hr (Note 2). The solution is acidified to pH 4 (2 N hydrochloric acid) and extracted into diethyl ether (4 x 50 mL) (Note 3). The organic layer is dried (MgSO₄) and concentrated under reduced pressure to afford 13.75 g of yellow oil (Note 4) which is subjected to flash column chromatography (1.5:1 hexanes-diethyl ether) to afford initially methyl (E)-3-(benzenesulfonyl)prop-2-enoate (400 mg, 2.9%) and then the desired Z-isomer (10.89 g, 81%) as a pale yellow solid, pure by spectral study (Note 5).

2. Notes

1. All reagents were purchased from Aldrich Chemical Company, Inc. and were used without further purification.

2. A magnetic stirrer is usually adequate. An overhead stirrer was used for the larger scale reported here.

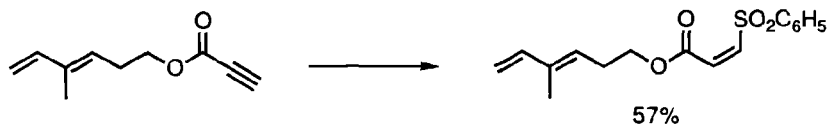
3. Slightly increased yields are observed if most of the organic material is removed under reduced pressure prior to extraction into ether.

4. Purity determines the structure of the product; the crude product is often a yellow solid at this point.

5. The isolated yield has ranged between 71 and 88%. The product has the following spectral and physical characteristics: mp 50.5-51.5°C (ether); IR (CH_2Cl_2) cm^{-1} : 3040 (m), 1732 (s), 1630 (m), 1440 (s), 1340 (s), 1310 (s), 1145 (s); ^1H NMR (CDCl_3 , 360 MHz) δ : 3.92 (s, 3 H, CO_2CH_3), 6.52 (d, 1 H, $J = 11.5$), 6.57 (d, 1 H, $J = 11.5$), 7.55-8.05 (m, 5 H, Ar); ^{13}C NMR (CDCl_3 , 90.56 MHz) δ : 52.43 (q), 127.93 (d), 129.23 (d), 131.5 (d), 133.95 (d), 135.50 (d), 139.42 (s), 164.22 (s); m/z : Found M^+ 226.02890, $\text{C}_{10}\text{H}_{10}\text{O}_4\text{S}$ requires M^+ , 226.02998; 226 (M^+ , 5), 195 (16), 161 (10), 131 (12), 77 (80), 51 (100).

3. Discussion

This procedure describes the short, one-pot, high-yield preparation of methyl (Z)-3-(benzenesulfonyl)prop-2-enoate. This route is shorter than a previously reported preparation.² We have been able to apply this technique to the preparation of a highly functionalized sulfonyl acrylate, although the generality of this reaction has not been studied (eq. 1).³



(1)

Vinyl sulfones in general serve as excellent dienophiles in Diels-Alder reactions,⁴ and we⁵ and others^{2,4} have found the resultant cyclohexene to contain very useful functionality for further manipulation. Hence the vinyl sulfone moiety can serve as a synthon for ethylene,⁶ terminal olefins,⁷ acetylene,⁸ and vinylsilanes⁹ in [4+2]-cycloadditions as well as valuable synthetic intermediates in general.¹⁰

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methyl (Z)-3-(benzenesulfonyl)prop-2-enoate: 2-Propenoic acid, 3-(phenylsulfonyl) methyl ester, (Z)- (11); (91077-67-7)

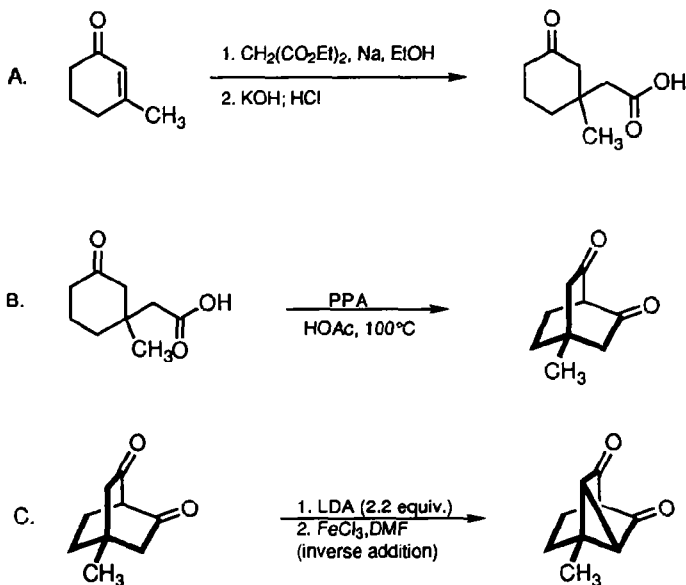
Methyl propiolate: Propiolic acid, methyl ester (8); 2-Propynoic acid, methyl ester (9 (922-67-8)

Sodium benzenesulfinate: Benzenesulfinic acid, sodium salt (8,9); (873-55-2)

INTRAMOLECULAR OXIDATIVE COUPLING OF A BISENOLATE:

4-METHYLTRICYCLO[2.2.2.0^{3,5}]OCTANE-2,6-DIONE

(Tricyclo[3.2.1.0^{2,7}]octane-6,8-dione, 2-methyl-)



Submitted by Marc-André Poupart, Gilbert Lassalle, and Leo A. Paquette.¹

Checked by L. A. Stolz and Robert K. Boeckman, Jr.

1. Procedure

A. *3-Methylcyclohexanone-3-acetic acid.* A 2-L, three-necked Morton flask fitted with a low-temperature thermometer, 250-mL addition funnel, an exit tube attached to a calcium chloride drying tube, and a Teflon-coated magnetic stirring bar, is charged with 1.1 L of anhydrous ethanol. The stirred solution is cooled to 0°C and

23 g (1 mol) of sodium cut into small pieces is added through the exit tube. During the addition, the temperature of the reaction mixture increases; therefore, cooling is applied (Note 1). After all of the sodium has completely reacted, 160.2 g (1 mol) of neat diethyl malonate is slowly added through the addition funnel while the temperature is maintained at 0°C (Note 2). At this point, 110.2 g (1 mol) of 3-methyl-2-cyclohexen-1-one (Note 3) is gradually introduced through the addition funnel at 0°C. A white precipitate eventually appears. After 9 days of stirring, the brown reaction mixture is poured onto ice, brought to neutrality with concentrated hydrochloric acid while being vigorously stirred, and extracted with one 600-mL portion and four 300-mL portions of ether (Note 4). The combined organic layers are washed with three 250-mL portions of saturated brine and dried over anhydrous magnesium sulfate. After evaporation under reduced pressure to remove the solvent, the residual oil is distilled through a 20-cm Vigreux column under reduced pressure. The first fraction (bp <60°C at 0.15 mm) consists of a mixture of unreacted starting materials. The second fraction (bp 145-165°C at 1.5 mm), a mixture of diesters (Note 5), is a colorless oil: 202-205 g (74-76%).

In a 2-L, one-necked, round-bottomed flask fitted with a magnetic stirring bar is placed 99 g (0.366 mol) of the diesters. A 1.0-M solution of potassium hydroxide (750 mL, 0.75 mol) is added to the flask with stirring. The mixture is stirred overnight and subsequently heated to reflux for 1 hr. After the mixture is cooled, it is acidified with 100 mL of concd hydrochloric acid and gently boiled for 20 min. Following return to room temperature, the mixture is transferred to a 2-L separatory funnel and extracted with dichloromethane (6 x 100 mL). The combined organic layers are washed with saturated brine (100 mL) and dried over sodium sulfate. The solvent is removed in a rotary evaporator and the residue is distilled in a Kugelrohr apparatus (140-160°C and 0.3-0.5 mm) to provide 49.3 g (79%) of the keto acid (Note 6).

B. 4-Methylbicyclo[2.2.2]octane-2,6-dione. A 2-L, three-necked, Morton flask fitted with a mechanical stirrer, a thermometer, and a reflux condenser, is charged with 245.0 g of polyphosphoric acid (PPA, Note 7), 26.8 g (158 mmol) of the keto acid, and 427 mL of glacial acetic acid. The vigorously stirred mixture is heated at 100°C for 7 hr. After being cooled, the reaction mixture is diluted with 500 mL of saturated brine and extracted with four 200-mL portions of benzene (Note 8). The combined organic layers are washed with saturated sodium bicarbonate (4 x 100 mL) and brine (1 x 100 mL) solutions, and dried over anhydrous magnesium sulfate. After removal of the solvents on a rotary evaporator, the viscous residue is distilled under reduced pressure in a Kugelrohr apparatus, affording 11.0-13.3 g (46-55%) of cyclized diketone as a colorless liquid, bp 100°C at 0.1 mm, which on standing at room temperature may solidify (Note 9).

C. 4-Methyltricyclo[2.2.2.0^{3,5}]octane-3,5-dione. A 500-mL, one-necked, round-bottomed flask fitted with a Teflon-coated magnetic stirring bar and a rubber septum is charged under nitrogen with a solution of 30.8 mL (220 mmol) of dry diisopropylamine in 170 mL of anhydrous tetrahydrofuran. The solution is cooled to 0°C (acetone-dry ice bath) and 137.5 mL (220 mmol) of a 1.6 M solution of *n*-butyllithium in hexanes is introduced over a 35-min period. The resulting colorless solution is stirred for 15 min at 0°C and then cooled to -78°C.

The diketone (15.20 g, 100 mmol) is dissolved in 27 mL of dry tetrahydrofuran in a 50-mL, round-bottomed flask and added dropwise through a 16-gauge cannula (nitrogen pressure) during 35 min to the lithium diisopropylamide solution. This mixture is stirred for 30 min at -78°C and is added in turn to 280.4 mL (300 mmol) of a 1.07 M solution of anhydrous ferric chloride (Note 10) in dry dimethylformamide diluted with 39 mL of dry dimethylformamide and contained in a 1-L, three-necked, round-bottomed flask equipped with an efficient mechanical stirrer and cooled to -78°C (Note 11). This addition is accomplished as rapidly as possible through an 8-gauge cannula

(nitrogen pressure). After the reaction mixture is stirred for 2 hr at -78°C , it is quenched by the dropwise addition of 24 mL of dry methanol and allowed to reach room temperature. Saturated brine (300 mL) is added and the entire mixture is filtered through Celite. The aqueous phase is extracted with four 250-mL portions of ether. The combined organic layers are washed with saturated brine (3 x 150 mL) and dried over anhydrous magnesium sulfate. After solvent evaporation under reduced pressure, the residue is chromatographed (100 g of TLC grade silica gel; eluant is 15% ethyl acetate in petroleum ether). There is isolated 6.4-6.5 g (43%, Note 12) of the cyclized diketone as a colorless oil (Note 13) and 1.11 g (7.3%) of starting material.

2. Notes

1. Cooling should be applied to moderate the reaction while maintaining a vigorous evolution of gas or the reaction time is prolonged unduly.

2. Cooling below 0°C will induce precipitation of the sodium diethyl malonate.

3. 3-Methyl-2-cyclohexen-1-one can be purchased from the Aldrich Chemical Company, Inc. or prepared according to a known procedure.² Checkers obtained material from Aldrich Chemical Company, Inc. and Lancaster Synthesis, Inc.

4. The checkers employed 600 mL of ether in the first extraction to ensure separation of the phases.

5. According to the literature,³ these esters consist of the product of Michael addition to 3-methylcyclohexenone and of an isomer arising from rearrangement of this primary adduct.

6. The keto acid exhibits the following spectral properties: IR (neat) cm^{-1} : 3500-2500, 1730, 1705; ^1H NMR (300 MHz, CDCl_3) δ : 1.07 (s, 3 H), 1.61-1.77 (m, 2 H), 1.77-1.97 (m, 3 H), 2.14-2.44 (m, 5 H), 8.4-10 (br s, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ : 21.8, 25.3, 35.7, 38.0, 40.7, 45.4, 53.0, 176.9, 179.7.

7. Polyphosphoric acid can be prepared by the addition of 200 g of phosphorus pentoxide (P_2O_5) to 100 mL of an 85% solution of phosphoric acid and heating to 170°C with vigorous stirring until all of the P_2O_5 is dissolved (ca. 6 hr).

8. Continuous extraction of the aqueous phase with toluene can also be applied for 3 days in order to yield 80% of the diketone after Kugelrohr distillation.

9. The pure diketone is a colorless solid, mp 75-76°C; IR (neat) cm^{-1} : 1735, 1710; 1H NMR (300 MHz, $CDCl_3$) δ : 1.17 (s, 3 H), 1.67-1.73 (m, 2 H), 2.07-2.13 (m, 2 H), 2.22 (ABq, 4 H, $J_{AB} = 8.0$, $\Delta\nu_{AB} = 35.05$), 3.16 (t, 1 H, $J = 2.9$); ^{13}C NMR (75 MHz, $CDCl_3$) δ : 22.7, 25.7, 31.0, 33.9, 50.4, 63.4, 206.6.

10. The 1.07 M anhydrous ferric chloride solution in dimethylformamide is prepared as follows: 178.43 g (1.1 mmol) of anhydrous solid ferric chloride is refluxed over 360 mL of thionyl chloride for 4 days at atmospheric pressure. After the solution is cooled, thionyl chloride is removed by distillation at 20 mm and trapped in a 1-L, round-bottomed flask cooled to -78°C. The solid residue is stirred for 1 hr at room temperature under reduced pressure (ca. 20 mm) and heated at 40°C for 1 hr under high vacuum (ca. 1 mm). Drying without heating is then continued overnight under high vacuum. The flask is filled with argon and cooled to 0°C. Approximately 600 mL of freshly distilled dimethylformamide is then slowly added (exothermic reaction). The entire dissolution of solid ferric chloride is achieved in an ultrasound bath during 24 hr. After decantation, the dark brown solution is transferred under argon to a 1-L volumetric flask and the required level is adjusted with freshly distilled dimethylformamide.

11. The checkers found that vigorous mechanical stirring was required because of the viscosity of the dimethylformamide solution at -78°C; otherwise, diminished yields were observed.

12. The yields obtained range from 40 to 54% depending principally on the rate of the inverse addition and the scale of the reaction.

13. The tricyclic diketone, a colorless oil which slowly solidifies, exhibits mp 34.5-35.0°C; IR (neat) cm^{-1} : 1760, 1710; ^1H NMR (300 MHz, CDCl_3) δ : 1.26 (s, 3 H), 2.00-2.06 (m, 2 H), 2.27-2.30 (m, 2 H), 2.46-2.68 (m, 1 H), 2.68 (d, 2 H, $J = 1.3$); ^{13}C NMR (75 MHz, CDCl_3) δ : 23.3, 26.6, 30.9, 47.1, 48.9, 52.6, 203.5.

3. Discussion

The initial Michael addition step is a modified and improved version of a procedure originally developed by Farmer and Ross.³ The second step involving acid-catalyzed dehydration of the cyclohexanone-3-acetic acid is adapted from earlier work developed for the desmethyl series.⁵

The intermolecular dimerization of ketone enolates to give 1,4-diketones has been accomplished earlier with cupric^{6,7} and ferric salts.⁸ These transition metal salts have also been used to achieve intramolecular carbon-carbon bond formation.^{7,9,10} However, step C represents the only reported example¹¹ of cyclopropane construction via technology of this type.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

4-Methyltricyclo[2.2.2.0^{3,5}]octane-2,6-dione: Tricyclo[3.2.1.0^{2,7}]octane-6,8-dione,
2-methyl- (12); (119986-99-1)

3-Methylcyclohexanone-3-acetic acid: Cyclohexaneacetic acid, 1-methyl-3-oxo-, (±)-
(12); (119986-97-9)

Diethyl malonate; Malonic acid, diethyl ester (8); Propanedioic acid, diethyl ester (9);
(105-53-3)

3-Methyl-2-cyclohexen-1-one: 2-Cyclohexen-1-one, 3-methyl- (8,9); (1193-18-6)

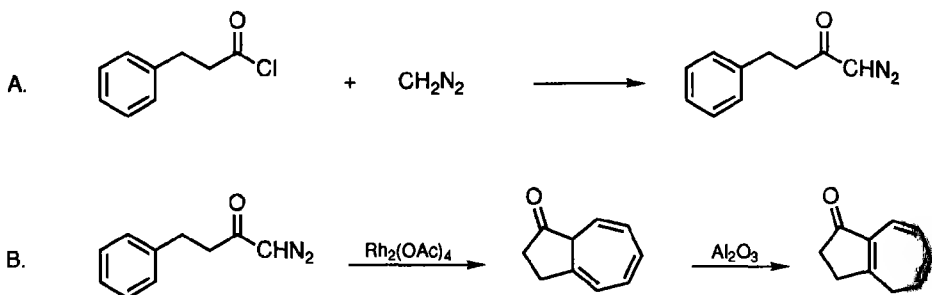
4-Methylbicyclo[2.2.2]octane-2,6-dione: Bicyclo[2.2.2]octane-2,6-dione,
4-methyl- (12); (119986-98-0)

Polyphosphoric acid (8,9); (8017-16-1)

DIAZO KETONE CYCLIZATION ONTO A BENZENE RING:

3,4-DIHYDRO-1(2H)-AZULENONE

(1(2H)-Azulenone, 3,4-dihydro-)



Submitted by Lawrence T. Scott and Chris A. Sumpter.¹

Checked by John M. Fevig and Larry E. Overman.

1. Procedure

Caution! Diazomethane is toxic and explosive; all operations should be carried out in a well-ventilated hood with adequate shielding (Note 1).

A. *1-Diazo-4-phenyl-2-butanone.* A 1-L Erlenmeyer flask equipped with a two-inch magnetic stirring bar and a two-hole rubber stopper fitted with a 125-mL Teflon stopcock separatory funnel (Note 2) and a drying tube filled with potassium hydroxide (Note 3) is charged with a solution of 200 mmol (3.4 equiv) of diazomethane (Note 4) in 600 mL of dry ether. The solution is cooled to 0°C and stirred at high speed (Note 5). To this cooled solution, 10.0 g (59 mmol) of hydrocinnamoyl chloride (3-phenylpropionyl chloride) (Note 6) diluted to 125 mL with anhydrous ether is added dropwise over a 1-hr period. The resulting reaction mixture is stirred cold for an additional 0.5 hr and then at room temperature for 1 hr. After this period of time the

reaction is complete, and excess diazomethane is removed by evacuating the Erlenmeyer flask with a water aspirator pump in the hood (Note 7). The Erlenmeyer flask is evacuated by connecting the aspirator to a one-hole stopper that has been fitted with a plastic or fire-polished glass tube. After the diazomethane has been removed, the remaining ethereal solution is concentrated by rotary evaporation to give 10.5-10.6 g (> 100% crude yield) of 1-diazo-4-phenyl-2-butanone as a yellow oil (Note 8). This oil is used without purification for the next reaction.

B. 3,4-Dihydro-1(2H)-azulenone. A 250-mL, one-necked round-bottomed flask is equipped with an egg-shaped magnetic stirring bar and a high dilution trident (Figure 1)⁴ (Note 9). The high dilution trident is further equipped with a 100-mL pressure-equalizing addition funnel attached to a nitrogen inlet and an efficient reflux condenser attached to a nitrogen outlet. The round-bottomed flask is charged with 100 mL of dry freshly distilled methylene chloride and 12 mg of rhodium diacetate dimer (Note 10). This heterogeneous mixture is stirred at high speed (Note 11) and heated to a rapid reflux without bumping. The addition funnel is charged with a solution of 8.7 g (50 mmol) of 1-diazo-4-phenyl-2-butanone (Note 12) diluted to 50 mL with methylene chloride. As soon as the high dilution trident reservoir (20 mL) fills up and begins to overflow back into the round-bottomed flask, dropwise addition of the diazo ketone solution is initiated (1:20, one drop of diazo ketone solution to every 20 drops of solvent entering the trident reservoir from the condenser). After the addition is complete (2.5-3 hr), the reaction mixture is allowed to reflux for an additional 1 hr. The reaction mixture is then cooled, and the yellow-green solution of the initially-formed unstable trienone (Note 13) is suction-filtered through 110 g of neutral alumina (Note 14) in a 250-mL fritted glass funnel to isomerize the β,γ -double bond into conjugation with the carbonyl group and to remove the rhodium diacetate dimer. The alumina is then washed with 100 mL of ethyl acetate, and the combined organic filtrates are concentrated by rotary evaporation to give a yellow oil. Vacuum distillation of this oil

through a short path distillation head gives 5.5-5.7 g (75-78% yield) of a colorless to slightly green oil that solidifies at 0°C, bp 73-75°C/0.2 mm (Note 15). This material is sufficiently pure for most purposes (Note 16). Recrystallization from hexane (80 mL per gram of trienone) yields colorless needles, mp 28.5-29.0°C (Note 17).

2. Notes

1. See full warning in *Org. Synth., Coll. Vol. II* **1943**, 165, and *Aldrichimica Acta* **1983**, 16(1), 3-10.

2. Ground glass can cause explosions; therefore, a Teflon stopcock must be used.

3. Potassium hydroxide must be used as the drying agent since calcium sulfate and other drying agents can react with diazomethane and cause an explosion.

4. Diazomethane is prepared as described in *Org. Synth., Coll. Vol. IV* **1963**, 250, with 50 g of Diazald (from Aldrich Chemical Company, Inc.) in 300 mL of ether added to 15 g of KOH in 25 mL of water, 30 mL of ether, and 50 mL of 2-(2-ethoxy-ethoxy)ethanol. One equivalent of diazomethane becomes incorporated in the reaction product, and the remainder serves as a scavenger for the HCl produced as a reaction by-product. The excess of diazomethane called for in this procedure is necessary to inhibit the undesired formation of 1-chloro-4-phenyl-2-butanone. The submitters report that this reaction can be performed on twice this scale with comparable results.

5. The high rate of stirring reduces the production of 1-chloro-4-phenyl-2-butanone, a by-product of this reaction.

6. This compound can be purchased from Aldrich Chemical Company, Inc. or prepared according to standard methods.²

7. Two hundred milliliters of ether and diazomethane are removed before transfer for rotary evaporation. Diazomethane in a rotary evaporator can cause explosions.

8. A pure sample of diazo ketone can be obtained by chromatography on silica gel using 15% ethyl acetate/hexane as an eluent, $R_f = 0.37$. The checkers estimate the purity of the crude diazo ketone to be 90-91% based on careful column chromatography of 1.0-g aliquots. They further estimate that approximately 5-6% of 1-chloro-4-phenyl-2-butanone is also produced in the reaction. The spectral properties of 1-diazo-4-phenyl-2-butanone are as follows: ^1H NMR (300 MHz, CDCl_3) δ : 2.59-2.64 (m, 2 H), 2.95 (t, 2 H, $J = 7$) 5.20 (broad s, 1 H), 7.17-7.31 (m, 5 H).

9. The high dilution trident in this example dilutes the diazo ketone solution to 10^{-3} - 10^{-4} M before it reaches the reaction mixture.

10. The rhodium diacetate dimer is used in catalytic amounts; 0.132% (weight of dimer/weight of diazo ketone) has worked out to be the best ratio for this reaction.

11. The high speed stirring minimizes undesired bimolecular reactions.

12. The submitters report that this step can be performed on a 0.5-mol scale (87 g of diazo ketone) in 86.5-94.9% yield. This amount of diazo ketone was prepared in multiple batches as described in Step A. The submitters were reluctant to prepare and handle diazomethane on a scale large enough to make 0.5 mol of diazo ketone in one batch.

13. The initially-formed trienone isomerizes quantitatively to β -tetralone on treatment with catalytic amounts of trifluoroacetic acid. This acid sensitivity precludes chromatography of the crude product on normal silica gel.

14. F20 alumina (60-200 mesh) from Schoofs, Inc. was used. The checkers used chromatography grade neutral alumina (100-125 mesh) supplied by Fluka.

15. The oil bath temperature maximum must be maintained below 120°C or the yield of product drops.

16. The checkers found that on this scale a bulb-to-bulb (Kugelrohr) distillation could also be employed. The distilled product is contaminated with approximately 4-5% of 1-chloro-4-phenyl-2-butanone which was produced in Step A. This impurity is easily removed by recrystallization from hexane. Alternatively, this impurity can be removed at the diazo ketone stage by column chromatography. The use of purified diazo ketone in Step B affords purer distilled product, but this modification has no significant effect on the overall yield.

17. The spectral properties of 3,4-dihydro-1(2H)-azulenone are as follows: ^1H NMR (300 MHz, CDCl_3) δ : 2.50 (narrow m, 2 H), 2.70 (narrow m, 2 H), 2.78 (apparent d, 2 H, $J = 6$), 5.38 (dt, 1 H, $J = 9.6, 6.3$), 6.09 (dd, 1 H, $J = 9.2, 6.2$), 6.47 (dd, 1 H, $J = 11, 5.7$), 6.68 (d, 1 H, $J = 11$); IR (film) cm^{-1} : 1697.

3. Discussion

The cyclopropanation of alkenes, alkynes, and aromatic compounds by carbenoids generated in the metal-catalyzed decomposition of diazo ketones has found widespread use as a method for carbon-carbon bond construction for many years, and intramolecular applications of these reactions have provided a useful cyclization strategy. Historically, copper metal, cuprous chloride, cupric sulfate, and other copper salts were used most commonly as catalysts for such reactions; however, the superior catalytic activity of rhodium(II) acetate dimer has recently become well-established.³ This commercially available rhodium salt exhibits high catalytic activity for the decomposition of diazo ketones even at very low catalyst:substrate ratios (< 1%) and is less capricious than the old copper catalysts. We recommend the use of rhodium(II) acetate dimer in preference to copper catalysts in all diazo ketone decomposition reactions. The present synthesis describes a typical cyclization procedure.

A special feature of the synthesis described here is the glass apparatus used to achieve high-dilution reaction conditions (Figure 1).⁴ This "trident" is simple but effective and can be fabricated quite easily from standard parts. The one shown here is designed to accept an overhead mechanical stirrer.

The product of this synthesis is an especially useful, highly functionalized hydroazulene that is not available commercially. We have used it as a synthetic precursor to homoazulene,⁵ and to a variety of homoazulene derivatives,⁶ bridged homotropylium cations,⁷ and azulene quinones.⁸ It could undoubtedly serve as a precursor to numerous natural products. The cyclization reaction tolerates electron-donating substituents^{3,9} but not halogens¹⁰ on the aromatic ring.

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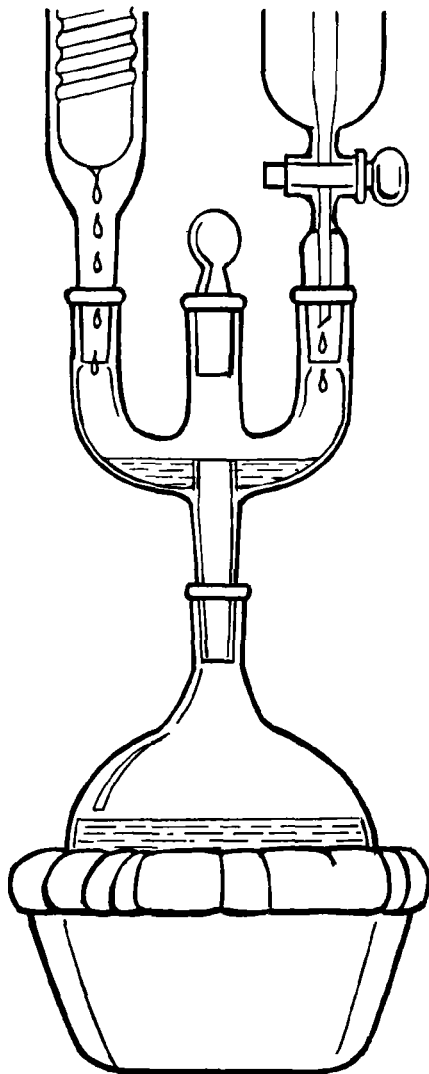
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Appendix

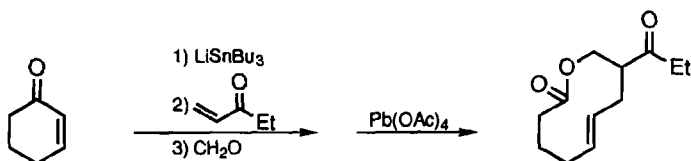
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3,4-Dihydro-1(2H)-azulenone: 1(2H)-Azulenone, 3,4-dihydro- (9); (52487-41-9)
 1-Diazo-4-phenyl-2-butanone: 2-Butanone, 1-diazo-4-phenyl- (8,9); (10290-42-3)
 Diazomethane: Methane, diazo- (8,9); (334-88-3)
 Diazald: p-Toluenesulfonamide, N-methyl-N-nitroso- (8); Benzenesulfonamide,
 N, 4-dimethyl-N-nitroso- (19); (80-11-5)
 2-(2-Ethoxyethoxy)ethanol: Ethanol, 2-(2-ethoxyethoxy) - (8,9); (111-90-0)
 Hydrocinnamoyl chloride (8); Benzenepropanoyl chloride (9); (645-45-4)
 Rhodium diacetate dimer: Acetic acid, rhodium(2+) salt (8,9); (5503-41-3)

Figure 1



**A GENERAL METHOD FOR THE PREPARATION OF 9-, 10-, AND
11-MEMBERED UNSATURATED MACROLIDES: SYNTHESIS OF
8-PROPIONYL-(E)-5-NONENOLIDE
(2H-Oxecin-2-one, 3,4,5,8,9,10-hexahydro-9-(1-oxopropyl)-, (E)-)**



Submitted by Kevin S. Webb, Edward Asirvatham, and Gary H. Posner.¹

Checked by Thais Sielecki and Albert I. Meyers.

1. Procedure

Caution! Benzene has been identified as a carcinogen: OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and gloves should be worn.

A flame-dried (Note 1), 500-mL, three-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, rubber septa, and an argon inlet is charged with 75 mL of anhydrous tetrahydrofuran (Note 2) and 8.0 mL (57.1 mmol) of diisopropylamine (Note 3), then cooled to -10°C via an ice/salt bath. Next 34.8 mL (55.0 mmol) of butyllithium (1.58 M, Note 4, in hexane) is added dropwise (over 4 min) to the vigorously stirred diisopropylamine solution, and stirred at -10°C for 20 min. Tributyltin hydride (15.2 mL, 55.0 mmol, Note 5) is added dropwise over 5 min to the solution, and the reaction mixture is stirred under argon at -10°C to 0°C for an additional 30 min. The flask is cooled to -78°C and stirred for 20 min.

A flame-dried (Note 1), 100-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, rubber septum, and an argon inlet is charged with 50 mL of anhydrous tetrahydrofuran (Note 2) and 4.85 mL (50.1 mmol) of 2-cyclohexen-1-one (Note 6), and cooled to -78°C . This solution (54.85 mL) is cannulated into the tributyltinlithium solution dropwise over 8 min (Note 7), and the solution is stirred at -78°C under argon for 25 min (Note 8). The same 100-mL, round-bottomed flask is charged with 50 mL of anhydrous tetrahydrofuran (Note 2) and 6.1 mL (59.4 mmol) of ethyl vinyl ketone (Note 9), and cooled to -78°C . This solution (56.1 mL) is cannulated into the 500-mL, round-bottomed flask dropwise over 8 min (Note 10), and the solution is stirred for 1.5 hr (Note 11). The resulting solution is then transferred from a -78°C cold bath to a -23°C cold bath (Note 12) and stirred at this temperature for 30 min.

A flame-dried (Note 1), 100-mL, three-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, Teflon stopcock, rubber septa, and an argon inlet is charged with 6 g of paraformaldehyde (Note 13). The flask is heated to $165\text{--}170^{\circ}\text{C}$ and the gaseous formaldehyde is bubbled into the -23°C solution (Note 14). After 15 min all of the paraformaldehyde is pyrolyzed (Note 15), and the solution becomes slightly cloudy and yellow. The 500-mL, three-necked, round-bottomed flask is transferred to a -40°C bath (maintained by a Flexicool cryostat) and allowed to stir under argon for 20 hr. The reaction mixture is quenched at -40°C with 7 mL of saturated ammonium chloride followed by 8 mL of distilled water. It is warmed to room temperature, poured into a 500-mL separatory funnel, and diluted with 75 mL of water; the organic layer is separated, and the aqueous layer is extracted with diethyl ether (2 x 100 mL). The combined organic layers are dried over anhydrous magnesium sulfate, filtered, and concentrated (Note 16) to afford 29.30 g of crude product.

A flame-dried (Note 1), 1000-mL, three-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, rubber septa, 24/40 condenser, and an argon inlet is charged with 300 mL of anhydrous benzene (Note 17), and 29.00 g (65.4

mmol) of lead tetraacetate (Note 18). The suspension is heated to 80°C and stirred vigorously under argon. A flame-dried (Note 1), 250-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, rubber septa, and an argon inlet is charged with 150 mL of anhydrous benzene (Note 17) and 29.30 g of the crude reaction mixture. This solution is cannulated into the lead tetraacetate suspension over 2 min (Note 19), and the suspension is allowed to reflux for 2.5 hr. The reaction flask is cooled to room temperature, quenched with 200 mL of distilled water, poured into a 2-L separatory funnel, and diluted with 1000 mL of diethyl ether (Note 20). The organic layer is washed with saturated sodium bicarbonate solution (3 x 200 mL), aqueous 5% hydrochloric acid (2 x 200 mL), distilled water (200 mL) and brine (200 mL). The organic layer is dried over anhydrous magnesium sulfate and filtered; solvent removal afforded 28.95 g of a crude oil. This crude residue (light yellow-brown oil) is purified by short-path column chromatography (Note 21) to yield 4.37 g (41.5%) of 8-propionyl-(E)-5-nonenolide (Notes 22 and 23).

2. Notes

1. All glassware and Teflon-coated magnetic stirring bars were flame-dried under vacuum (0.5 mm) for 5 min, then back-filled with argon. The procedure was repeated a total of three times.

2. Baker reagent grade tetrahydrofuran (99% obtained from Aldrich Chemical Company, Inc.) was distilled over sodium metal spheres/benzophenone under an inert atmosphere and used immediately.

3. Diisopropylamine, 99%, was obtained from Aldrich Chemical Company, Inc., and allowed to reflux over calcium hydride (95+% obtained from Aldrich Chemical Company, Inc.) for 24 hr prior to use.

4. Butyllithium in hexane (1.6 M), obtained from Aldrich Chemical Company, Inc., was titrated (using 2,5-dimethoxybenzyl alcohol as the indicator²) just prior to use.

5. Tributyltin hydride, 97%, was obtained from Aldrich Chemical Company, Inc., and must be used quickly to insure generation of the tributyltinlithium species. Two minutes after the initial addition of tributyltin hydride the colorless solution turned light yellow.

6. 2-Cyclohexen-1-one, 97%, was obtained from Aldrich Chemical Company, Inc., and was freshly distilled via short-path distillation.

7. After the 2-cyclohexenone addition was complete, the 100-mL, round-bottomed flask was washed with 10 mL of anhydrous tetrahydrofuran, and this wash was cannulated into the 500-mL flask (Note 2).

8. A small aliquot of the reaction mixture was removed after 15 min and analyzed by analytical TLC. The TLC was developed in 20% ethyl acetate:hexane and showed that the 1,4-conjugate addition had proceeded to completion ($R_f = 0.58$); the solution was colorless at this point of the reaction.

9. Ethyl vinyl ketone, 97%, was obtained from Aldrich Chemical Company, Inc., and used directly.

10. The reaction mixture turned slightly yellow during addition of ethyl vinyl ketone.

11. A small aliquot was removed from the reaction mixture and analyzed by analytical TLC (20% ethyl acetate:hexane) to insure that the Michael addition had proceeded, $R_f = 0.44$, and $R_f = 0.32$ corresponding to the diastereomeric intermediates.

12. A -23°C bath was obtained from a mixture of dry ice/carbon tetrachloride. A temperature between -40°C and -20°C is necessary.

13. Paraformaldehyde, 95%, was obtained from Aldrich Chemical Company, Inc., and used directly.

14. The argon inlet was equipped with a 16-gauge, 3-inch, syringe needle, the transfer cannula was a flex-needle (Z10,091-9) obtained from Aldrich Chemical Company, Inc., and the outlet bubbler was equipped with a 16-gauge, 3-inch, syringe needle.

15. A high pressure stream of argon was needed to prevent the gaseous formaldehyde from polymerizing to paraformaldehyde in the transfer flex-needle.

16. The weight of 29.30 g was achieved by attaching the round-bottomed flask to a vacuum (1.5 mm) and heating via a water bath (55°C) for 4 hr.

17. Benzene (thiophene-free, 99+%, 900 mL) was obtained from Aldrich Chemical Company, Inc., and washed with concentrated sulfuric acid (5 x 100 mL), distilled water (100 mL), aqueous 2% sodium hydroxide solution (100 mL), distilled water (100 mL), and dried over anhydrous magnesium sulfate. It was then allowed to reflux over calcium hydride for 24 hr. The checkers found that the benzene only needed to be distilled from calcium hydride.

18. Lead tetraacetate was purchased from Aldrich Chemical Company, Inc., and used directly.

19. The transfer cannula was a 12-inch, 16-gauge, double-tipped syringe needle, and the 250-mL flask was washed with an additional 30 mL of anhydrous benzene (Note 17), which was cannulated into the 1000-mL flask.

20. The 1000-mL, round-bottomed flask was washed with diethyl ether (3 x 100 mL of the 1000 mL).

21. Working on 1/2 of the present scale, the checkers found that by using Amicon Grace Matrex Silica Gel, (60 Å, 20-45 m) and an eluting solvent of 10% diethyl ether:hexane, 3.50 g (66.0%) of 8-propionyl-(E)-5-nonelide was obtained. The white solid was further purified by recrystallization from 15 mL of hexane to yield 3.15 g (60.0%) as a white solid.

22. The physical properties are as follows: IR (CHCl₃) cm⁻¹: 2933, 1731, 1349, 1210, 1154, 979, 770, 746; ¹H NMR (CDCl₃, 400 MHz) δ : 1.05 (t, 2 H, J = 7.2), 1.12 (t, 1 H, J = 7.2), 1.70-3.00 (m, 11 H), 3.76-3.82 (m, 0.67 H), 4.15-4.21 (m, 0.33 H), 5.05-5.70 (m, 3 H). When the proton signals at 1.90-2.90 ppm were irradiated, the two olefinic multiplets collapsed into two doublets (J = 15.2). An analytical sample (4.37 g) was recrystallized from 20 mL of hexane (Fisher, certified) to yield 4.05 g (38.5%) as a white solid: mp 70-71°C. Anal. Calcd for C₁₂H₁₈O₃: C, 68.57; H, 8.57. Found: C, 68.47; H, 8.68.

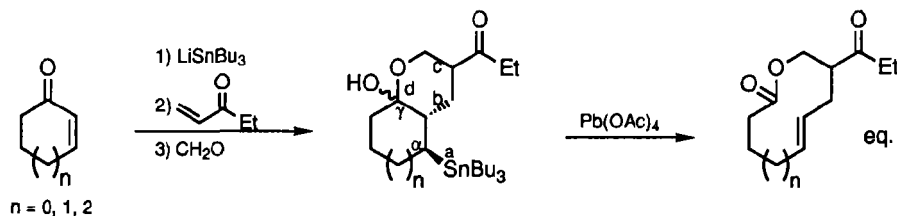
23. In order to determine whether the product was a mixture of geometrical isomers (e.g., differing by cis or trans geometry at the double bond) or conformers it was necessary to obtain ¹H NMR spectra at various temperatures. The 400 MHz ¹H NMR (DMSO-d₆) at 100°C shows that the two triplets (δ 1.05 and 1.12) start to collapse to one triplet, the multiplicity of the peaks in the region of δ 5.05-5.70 simplify greatly, and the initial peak ratios in the region of δ 3.70-4.20 change from 1:2 to 1:3. Therefore, the nonenolide is one pure isomer of only trans double bond geometry and is able to exist as two stable conformers in solution. The glass capillary GC (Hewlett Packard 5890) of 8-propionyl-(E)-5-nonenolide shows only one peak with a retention time of 4.21 min (injector temperature 175°C, detector temperature 225°C).

3. Discussion

The procedure described is a simple, rapid, and convenient method for conversion of n-sized cycloalkanones into n+4 alkenolides. Significant but limited progress has been reported in the recent literature toward the preparation of medium and large ring lactones via ring-expansion reactions. One of the most notable and useful developments in this area involves conversion of a cycloalkanone into a bicyclic vinylic ether which is oxidatively cleaved to form a ring-enlarged keto lactone.³

Recently, several variations of this ring-enlargement reaction have been reported including the scission of alkoxy radicals.⁴ In most of these cases, a superfluous functional group (e.g., ketone, iodide) is produced during cleavage of the bicyclic system. Regiospecific conversion of such functional groups into a specific alkene structural unit is usually not possible because of the similar chemical environment α and α' to the functional group.⁵ Because many regiospecifically unsaturated lactones are physiologically active natural products,⁶ we have developed methodology to prepare unsaturated macrolides having a carbon-carbon double bond with specific geometry and at a specific position in the macrolide skeleton.

Because of our interest in one-pot, multicomponent annulations,⁷ we envisioned a flexible and efficient protocol which would link the four different components via the formation of four new bonds (a-d, eq. 1) in one reaction vessel. The intermediate γ -hydroxystannanes thus formed in eq. 1 could be oxidatively fragmented⁸ to produce both ring enlargement and regiospecific formation of an alkenyl unit. This 4-atom ring expansion methodology of common sized α,β -unsaturated ketones has led to the syntheses of many mono- and disubstituted 9-, 10-, and 11-membered unsaturated macrolides (Table).

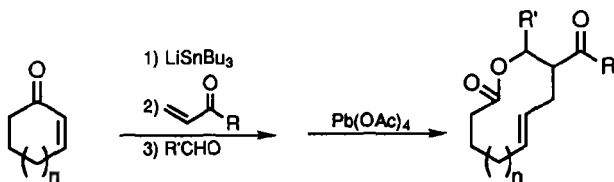


Based on the data in the Table and on our published results,⁷ it is clear that five-, six-, and seven-membered cycloalkenones undergo this 4-atom ring enlargement reaction to produce medium ring, unsaturated lactones in overall yields

of 30-54%. Permutations on this methodology include using either ethyl vinyl ketone or phenyl vinyl ketone as the third component, and either substituted acetaldehydes or substituted benzaldehydes as the last component. The geometrical assignment of the new carbon-carbon double bond was made from interpreting the 400 MHz ^1H NMR decoupled spectra in which each olefinic proton collapsed into a baseline resolved doublet with coupling constants of $J = 15\text{-}16$. The proton decoupling experiments conducted to determine the relative stereochemistry of the vicinal substituents in the disubstituted macrolides were inconclusive; often the magnitude of the coupling constants were similar or not discernible from the spectra. Therefore, the relative stereochemistry of the vicinal substituents was established by examining the ^1H NMR spectra of the intermediate γ -hydroxystannanes (usually only two were isolated). The trans-hemiketals showed typical coupling constants of $J = 8\text{-}13$, while the cis-hemiketals showed coupling constants of $J = 2\text{-}4$. Separate lead tetraacetate oxidative fragmentation of these γ -hydroxystannanes produced two different ring-enlarged lactones both with specific trans-double bond geometry and differing only in the relative stereochemistry of the vicinal substituents.

This homologous Baeyer-Villiger type oxidative ring expansion represents a conceptually new protocol illustrating the substantial value of one-pot, four-component annulations as a flexible and simple new synthetic method.

TABLE



n	R	R'	% Yield	trans:cis
0	Et	CH ₃	30.5	0.57
1	Et	CH ₃	47	0.7
1	Et	CH ₂ =CH	39.5	2.6
1	Et	o-BrC ₆ H ₄	47	5.3
1	Et	o-IC ₆ H ₄	37	2.6
1	Ph	o-IC ₆ H ₄	34	1.0
1	Et	PhCH ₂	43.5	1.5
1	Ph	o-BrC ₆ H ₄ CH ₂	30	1.0
1	Et	o-N(phtl)C ₆ H ₄	42	5.0
1	Et	H	41.5	
1	Et	2,3-(MeO) ₂ C ₆ H ₃ CH ₂	52	1.0
1	Ph	2,3-(MeO) ₂ C ₆ H ₃ CH ₂	51	1.5
1	Et	3-thienylCH ₂	52	0.7
1	Ph	3-thienylCH ₂	52	1.8
1	Et	3-furylCH ₂	54	0.7
1	Ph	3-furylCH ₂	40	7.0
2	Et	Cyclopropyl	53	1.1
2	Et	CH ₃	40	1.0
2	Et	3-(MeO)C ₆ H ₄	41.5	1.5
2	Ph	o-IC ₆ H ₄ CH ₂	38	1.9

1. The Johns Hopkins University, Department of Chemistry, Baltimore, MD 21218.
We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the NSF (CHE 86-07974) for financial support, and Professor S.-S. Jew for experimental help.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

8-Propionyl-(E)-5-nonenolide: 2H-Oxecin-2-one, 3,4,5,8,9,10-hexahydro-9-(1-oxopropyl)-, (E)- (12); (114633-68-0)

Diisopropylamine (8); 2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

Tributyltin hydride: Stannane, tributyl- (8,9); (688-73-3)

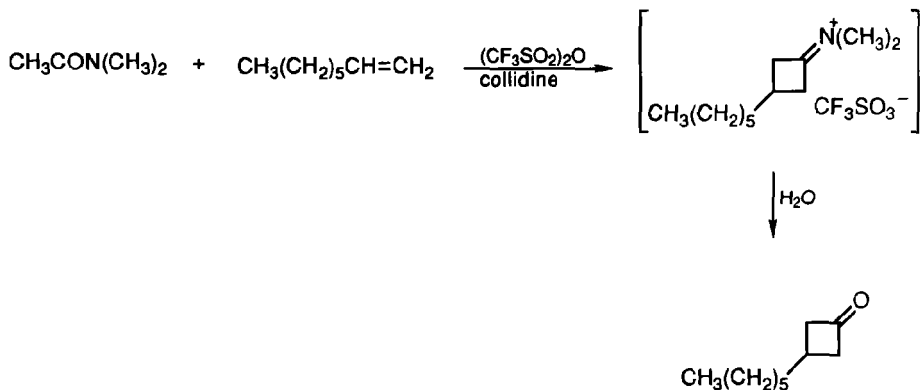
2-Cyclohexen-1-one (8,9); (930-68-7)

Ethyl vinyl ketone: 1-Penten-3-one (8,9); (1629-58-9)

Paraformaldehyde (9): (30525-89-4)

Lead tetraacetate: Acetic acid, lead (4+) salt (8,9); (546-67-8)

**A GENERAL SYNTHESIS OF CYCLOBUTANONES FROM OLEFINS
AND TERTIARY AMIDES: 3-HEXYLCYCLOBUTANONE**



Submitted by C. Schmit, J. B. Falmagne, J. Escudero, H. Vanlierde,
and L. Ghosez.¹

Checked by Thomas J. Sowin and Albert I. Meyers.

1. Procedure

A 500-mL, three-necked flask is equipped with a rubber septum, a magnetic stirring bar, a gas inlet, and a reflux condenser. The top of the condenser is connected to a pressure-equalizing dropping funnel isolated from moisture by a sulfuric acid trap (Note 1). The flask is cooled to -15°C and charged with N,N-dimethylacetamide (3.26 g, 37.5 mmol) (Note 2) in 100 mL of 1,2-dichloroethane (Note 3). The dropping funnel is charged with 1-octene (16.8 g, 150 mmol) (Note 4) and 2,4,6-collidine (5.44 g, 45 mmol) (Note 5) in 50 mL of 1,2-dichloroethane. A slightly positive pressure of argon is maintained in the apparatus throughout the course of the reaction.

Trifluoromethanesulfonic anhydride (12.69 g, 45 mmol) (Note 6) is added through the rubber septum into the solution of N,N-dimethylacetamide by means of a syringe. A precipitate is formed. The olefin-collidine solution is then added dropwise over a period of 20 min. During these operations rapid stirring and cooling are maintained. The resulting mixture is refluxed for 17 hr (Note 7). The solvent is removed by rotary evaporation. The oily residue is washed with dry ether (3 x 20 mL) (Note 8). Then 20 mL of carbon tetrachloride (Note 9) and 20 mL of water are added to the crude cyclobutaniminium salt. The mixture is refluxed for 6 hr (Note 10). The organic phase is separated and the aqueous phase is extracted with carbon tetrachloride (3 x 20 mL). The combined organic phases are dried over anhydrous magnesium sulfate. The solvent is removed by distillation at atmospheric pressure (Note 11). Bulb to bulb distillation (bath temperature 100-110°C, water pump) gives 3.3 g (59%) of 3-hexylcyclobutanone (Notes 12 and 13).

2. Notes

1. The assembled apparatus is flame dried under a slight pressure of argon.
2. N,N-Dimethylacetamide (Janssen Chimica, Beerse, Belgium) is distilled before use. The checkers used it as obtained from Aldrich Chemical Company, Inc.
3. 1,2-Dichloroethane (99%) is obtained from Janssen Chimica or Aldrich Chemical Company, Inc. It is distilled from calcium hydride.
4. 1-Octene (97%) is purchased from Janssen Chimica or Aldrich Chemical Company, Inc. and distilled.
5. 2,4,6-Collidine (99%, Janssen Chimica or Aldrich Chemical Company, Inc.) is distilled from calcium hydride and stored under argon in a brown bottle.

6. Trifluoromethanesulfonic anhydride is prepared just prior to use according to the procedure of Stang, et al.² The checkers obtained it from Aldrich Chemical Company, Inc.

7. During this period the solution turns dark brown and, after rotary evaporation, the residue is a thick, black oil. The progress of the reaction can be followed by IR ($\nu_{C=N^+}$) cm^{-1} : 1730-1735, but the checkers found that it was complete in this 17-hr period.

8. Technical ether is dried over potassium hydroxide.

9. Technical carbon tetrachloride is used. Dichloromethane is preferred only when the cyclobutanone is too volatile.

10. The progress of the hydrolysis can be followed by IR, but the checkers found that it was complete in 6 hr.

11. Rotary evaporation or vacuum distillation can lead to a substantial loss of cyclobutanone.

12. The spectral properties of the compound are as follows: IR (CCl_4 , $\nu_{C=O}$) cm^{-1} 1785; ^1H NMR (270 MHz, CDCl_3) δ : 0.840 (t, 3 H, CH_3), 1.226-1.243-1.302 (m, 8 H, CH_2), 1.513 (m, 2 H, CH), 2.300 (m, 1 H, CH), 2.610 (m, 2 H, CH), 3.079 (m, 2 H, CH); ^{13}C NMR (75.5 MHz, CDCl_3) δ : 13.98, 22.53, 23.78, 28.16, 29.02, 31.71, 36.29, 52.43, 208.61.

13. The physical properties of the semicarbazone are as follows: mp 148.5°C; Anal. Calcd for $\text{C}_{11}\text{H}_{21}\text{N}_3\text{O}$: C, 62.53; H, 10.02; N, 19.88; O, 7.57. Found: C, 62.63; H, 10.05; N, 19.95; O, 7.50.

3. Discussion

Cyclobutanones are important synthetic intermediates. A common synthetic method for their preparation is the [2+2] cycloaddition of olefins with ketenes often

generated in situ from acid chlorides. However, that method suffers limitations especially when aldoketenes and unreactive olefins are used.

Keteniminium salts are more electrophilic than ketenes and are thus able to react with less nucleophilic olefins. Ketoketeniminium salts can be conveniently prepared from the corresponding α -chloro enamines and Lewis acids.³ However, the method cannot be applied well to the preparation of the less stable aldoketeniminium salts.

The method described here which involves the in situ generation of keteniminium triflates is practical and more general. The best results were obtained with 2,4,6-collidine but occasionally the more expensive 2,6-di-*t*-butyl-4-methylpyridine was superior. Pyridine gave satisfactory results in few uses only. Triethylamine always gave poor results. With the more reactive olefins (e.g., styrene), reactions can be run in refluxing dichloromethane. The procedure described here usually gives better yields than that previously reported in a preliminary communication.⁴ It has been used to prepare cyclobutanones as well as cyclobutenones^{5,6} from a wide variety of olefins or acetylenes. A few examples are shown in Table I. The method works well for olefins or acetylenes bearing alkyl, alkenyl or aryl groups. It does not apply to enol ethers or enamines.

1. Laboratoire de Chimie Organique de Synthèse, Université Catholique de Louvain, Place Louis Pasteur 1, B-1348, Louvain-La-Neuve, Belgium.
2. Stang, P. J.; Dueber, T. E. *Org. Synth., Coll. Vol.* **6** **1988**, 757.
3. (a) Marchand-Brynaert, J.; Ghosez, L. *J. Am. Chem. Soc.* **1972**, *94*, 2870; (b) Sidani, A.; Marchand-Brynaert, J.; Ghosez, L. *Angew. Chem., Inter. Ed. Engl.* **1974**, *13*, 267; (c) Houge, C.; Frisque-Hesbain, A. M.; Mockel, A.; Declercq, J. P.; Germain, G.; Van Meersche, M. *J. Am. Chem. Soc.* **1982**, *104*, 2920; (d)

- Saimoto, H.; Houge, C.; Hesbain-Frisque, A.-M.; Mockel, A.; Ghosez, L. *Tetrahedron Lett.* **1983**, *24*, 2251.
4. Markó, I.; Ronsmans, B.; Hesbain-Frisque, A. M.; Dumas, S.; Ghosez, L.; Ernst, B.; Greuter, H. *J. Am. Chem. Soc.* **1985**, *107*, 2192.
5. Falmagne, J.-B.; Escudero, J.; Talbe-Sahraoui, S.; Ghosez, L. *Angew. Chem., Inter. Ed. Engl.* **1981**, *20*, 879.
6. (a) Hoornaert, C.; Hesbain-Frisque, A. M.; Ghosez, L. *Angew. Chem., Inter. Ed. Engl.* **1975**, *14*, 569; (b) Schmit, C.; Sahraoui-Taleb, S.; Differding, E.; Dehasse-De Lombaert, C. G.; Ghosez, L. *Tetrahedron Lett.* **1984**, *25*, 5043.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

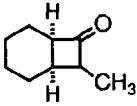
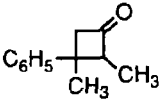
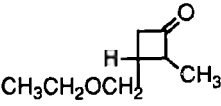
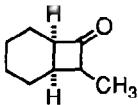
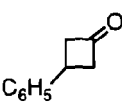
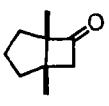
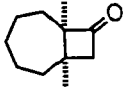
N,N-Dimethylacetamide: Acetamide, N,N-Dimethyl- (8,9); (127-19-5)

1-Octene (8,9); (111-66-0)

2,4,6-Collidine: Pyridine, 2,4,6-trimethyl- (8,9); (108-75-8)

Trifluoromethanesulfonic anhydride: Methanesulfonic acid, trifluoro-, anhydride (8,9); (358-23-6)

TABLE I
SYNTHESIS OF CYCLOBUTANONES FROM TERTIARY AMIDES AND OLEFINS

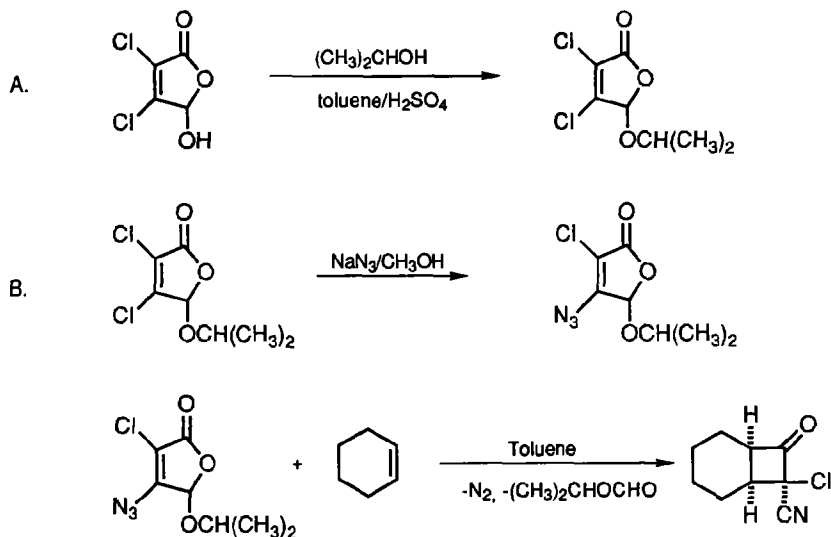
Amide	Olefin	Cyclobutanone	Yield %
$\text{CH}_3\text{CH}_2\text{CON}(\text{CH}_3)_2$	Cyclohexene		89 ^a
$\text{CH}_3\text{CH}_2\text{CON}(\text{CH}_3)_2$	α -Methylstyrene		79 ^a
$\text{CH}_3\text{CH}_2\text{CON}(\text{CH}_3)_2$	Allyl ethyl ether		56 ^a
$\text{CH}_3\text{CON}(\text{CH}_3)_2$	Cyclohexene		46
$\text{CH}_3\text{CON}(\text{CH}_3)_2$	Styrene		71
$(\text{H}_3\text{C})_2\text{NCO}-\underset{\text{CH}_3}{\text{CH}}(\text{CH}_2)_3\text{CH}=\text{CH}_2$			87 ^b
$(\text{H}_3\text{C})_2\text{NCO}(\text{CH}_2)_6\text{CH}=\text{CH}_2$			71 ^b

^aMixture of endo + exo isomers. ^bThese reactions were performed under slightly different conditions.⁴

7-CHLORO-7-CYANOBICYCLO[4.2.0]OCTAN-8-ONE

(Prepared from Chlorocyanoketene)

(Bicyclo[4.2.0]octane-7-carbonitrile, 7-chloro-8-oxo-, (1 α ,6 α ,7 β)-)



Submitted by Paul L. Fishbein and Harold W. Moore.¹

Checked by Steven Wolff and David L. Coffen.

1. Procedure

A. *3,4-Dichloro-5-isopropoxy-2(5H)-furanone*.² A 1-L, round-bottomed flask equipped with a Dean-Stark trap, condenser, argon bubbler, and magnetic stirrer is charged with 50.7 g (0.30 mol) of mucochloric acid (Note 1), 46 mL (0.60 mol) of isopropyl alcohol, 300 mL of toluene, and 20 drops of concd sulfuric acid. The mixture is heated to reflux with stirring overnight (~18 hr) with separation of water. The

solution is cooled, washed with saturated sodium bicarbonate solution and brine, and dried with magnesium sulfate. After removal of the solvent under reduced pressure, the residue is distilled to give 60.88 g (96%) of the furanone as a clear colorless liquid (bp 90-91°C, 1.5 mm; Lit.² mp 23-24°C, bp 109-111°C, 6 mm).

B. 7-Chloro-7-cyanobicyclo[4.2.0]octan-8-one. To a 250-mL Erlenmeyer flask is added 20.0 g (94.8 mmol) of 3,4-dichloro-5-isopropoxy-2(5H)-furanone and 120 mL of methanol. The flask is cooled in an ice bath with stirring and 7.5 g (115.4 mmol) of sodium azide is added. The ice bath is removed after 15 min and the mixture is stirred for an additional 50 min. After dilution with 600 mL of water, the reaction mixture is extracted with one 100-mL and two 50-mL portions of toluene. The combined organic layers are washed with water (2 x 100 mL) and with 100 mL of brine and are dried with magnesium sulfate. TLC analysis (1:1 ether:hexane, SiO₂) indicates only one component (*R_f* = 0.38) and no remaining dichlorofuranone (*R_f* = 0.45) (Note 3).

A 2-L, three-necked flask fitted with a condenser, argon bubbler, thermometer, and addition funnel is charged with 700 mL of toluene (freshly distilled and dried over 4 Å molecular sieves) and 20 mL (Note 4) of cyclohexene (freshly distilled). With magnetic stirring, the mixture is heated to 105°C and the azidofuranone solution prepared above is added over a period of 20 min (Note 5). Upon completion, the reaction mixture is heated for an additional 1.25 hr at 105°C. The solution is cooled and concentrated under reduced pressure to yield a yellow-brown residue which is distilled using a short-path apparatus to give 13.3 g (76%) (bp 85-90°C, 0.5 mm) of the cyclobutanone as a very pale yellow oil which solidifies (mp 34-35°C) upon standing at 4°C (Notes 6 and 7).

2. Notes

1. Practical grade mucochloric acid obtained from Aldrich Chemical Company, Inc. (mp 125-128°C) was used. Unless otherwise stated, all reagents and solvents were of commercial grade. The checkers used mucochloric acid obtained from Eastman Organic Chemicals.

2. The spectral properties are as follows: IR (CCl₄) cm⁻¹: 1795, 1652; ¹H NMR (CDCl₃) δ: 1.31 (d, 6 H, J = 6.2), 4.14 (heptet, 1 H, J = 6.2), 5.87 (s, 1 H); MS (EI): 195 (39), 151 (100), 95 (25); MS (CI): 211 (M+1), 100; Anal. Calcd. for C₇H₈Cl₂O₃: C, 39.84; H, 3.82. Found: C, 39.55; H, 3.84.

3. The submitters isolated and characterized the azidofuranone as a white crystalline solid after recrystallization from petroleum ether (bp 35-60°C), with mp 51.5-52.5°C. The spectral properties are as follows: IR (CCl₄) cm⁻¹: 2130, 1814, 1664; ¹H NMR (CDCl₃) δ: 1.33 (d, 6 H, J = 6.2), 4.17 (heptet, 1 H, J = 6.2), 5.99 (s, 1 H); MS (EI): 217 (M⁺, 6), 158 (34), 119 (28, C₃ClNO + H₂O), 101 (77), 73 (100); MS (CI): 218 (M+1, 55), 120 (10, C₃HClNO + H₂O), 102, (100). Anal. Calcd. for C₇H₈ClN₃O₃: C, 38.64; H, 3.71. Found: C, 38.67; H, 3.65. The azidofuranone decomposes at about 80°C so caution must be exercised when working with it.

4. If an alkene less volatile than toluene is used, 1.1-1.2 equiv of the alkene are satisfactory.

5. The ketene must be generated in situ since it is exceptionally reactive and will undergo self-condensation if permitted.

6. Recrystallization from petroleum ether (35-60°C) in a dry ice/acetone bath afforded colorless crystals with mp 39.5-40.5°C. The spectral properties are as follows: IR (CCl₄) cm⁻¹: 2340, 1838; ¹H NMR (CDCl₃) δ: 1.66 (m, 8 H), 3.03 (m, 1 H), 3.96 (m, 1 H); ¹³C NMR (CDCl₃): 20.72, 21.20, 21.41, 24.25, 36.26, 55.33, 64.17, 115.90, 189.91; MS (EI): 183 (M⁺, 6), 148 (46), 119 (13), 109 (33), 81 (100); MS (CI):

184 (M+1, 84), 156 (100). Anal. Calcd. for $C_9H_{10}ClNO$: C, 58.87; H, 5.49. Found: C, 58.58; H, 5.71.

7 Since chlorocyanocyclobutanones are readily hydrolyzed, protic recrystallization solvents and silica gel chromatography should be avoided. Short path distillation is the method of choice for the purification of most of the cyclobutanones.

3. Discussion

Chlorocyanoketene has been prepared previously by the thermal decomposition of the pseudomethyl ester of the azidofuranone.³ This azide has been used extensively without complication. However, all azides are capable of detonation. The ratio (C+O/N) has been suggested as a threshold value for detonation, which may occur when this ratio is lower than 3:1.⁴ The ratio for the previously used azide is 2.7 while that for the isopropyl analog is 3.3:1.

The synthesis of chlorocyanoketene presented here has advantages over other routes such as dehydrohalogenation of the appropriate acid chloride.⁵ The most obvious advantage is that the ketene is generated slowly during thermolysis. Thus, its concentration is always low. In addition, since it is generated by pyrolytic means, the presence of tert-amines and/or metals is avoided. No other method for the synthesis of chlorocyanoketene has been reported. However, we have found that it can be prepared with difficulty from chlorocyanoacetyl chloride.

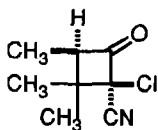
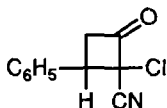
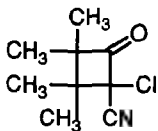
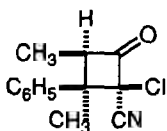
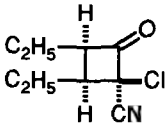
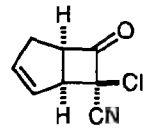
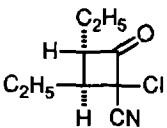
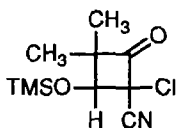
Chlorocyanoacetyl chloride can be made from the extremely hygroscopic acid. It is quite unstable, with 1 g decomposing in 1 hr at room temperature. If a mixture of an imine and triethylamine is treated with the acyl chloride only a dark tar is obtained. However, if the acyl chloride is first treated with the imine, the reaction allowed to subside, and the mixture then treated with triethylamine, the resulting 2-azetidinone is

formed in 63% yield. This is in comparison with the 96% yield obtained by using the azidofuranone.

Other cyclobutanones that can be made with chlorocyanoketene and their respective yields are shown in the Table.

1. Department of Chemistry, University of California, Irvine, CA 92717.
2. The procedure for making the pseudoester is from Hachihama, Y; Shono T. *J. Chem. Soc., Japan, Ind. Chem. Sect.* **1955**, *58*, 692; *Chem. Abstr.* **1956**, *50*, 12015e.
3. (a) Moore, H. W.; Hernandez, L.; Sing, A. *J. Am. Chem. Soc.* **1976**, *98*, 3728; (b) Kunert, D. M.; Chambers, R.; Mercer, F.; Hernandez, L., Jr.; Moore, H. W. *Tetrahedron Lett.* **1978**, 929; (c) Fishbein, P. L.; Moore, H. W. *J. Org. Chem.* **1984**, *49*, 2190.
4. Biffin, M. E. C.; Miller, J.; Paul, D. B. "Introduction of the Azido Group" In "The Chemistry of the Azido Group"; Patai, S., Ed.; Wiley: New York, 1971; p. 61.
5. Ward, R. W. "The Preparation of Ketenes" In "The Chemistry of Ketenes, Allenes, and Related Compounds, Part 1"; Patai, S., Ed.; Wiley: New York, 1980; pp. 223-227.

Table
Other Cyclobutanones From Chlorocyanoketene^{4c}

	80%		86%
	74%		86%
	93%		30%
	67%		70%

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

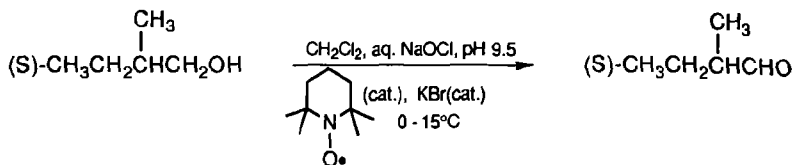
7-Chloro-7-cyanobicyclo[4.2.0]octan-8-one: Bicyclo[4.2.0]octane-7-carbonitrile, 7-chloro-8-oxo-, (1 α ,6 α ,7 β)- (11); (89937-15-5)

3,4-Dichloro-5-isopropoxy-2(5H)-furanone: 2(5H)-Furanone, 3,4-dichloro-5-isopropoxy- (8); 2(5H)-Furanone, 3,4-dichloro-5-(1-methylethoxy)- (9); (29814-12-8)

Mucochloric acid: Malealdehydic acid, dichloro- (8); 2-Butenoic acid, 2,3-dichloro-4-oxo-, (Z)- (9); (87-56-9)

Sodium azide (8,9); (26628-22-8)

**A GENERAL SYNTHETIC METHOD FOR THE OXIDATION OF PRIMARY
ALCOHOLS TO ALDEHYDES: (S)-(+)-2-METHYLBUTANAL
(Butanal, 2-methyl-, (S)-)**



Submitted by Pier Lucio Anelli, Fernando Montanari, and Silvio Quici.¹

Checked by Katsumasa Nonoshita and Hisashi Yamamoto.

1. Procedure

A 1-L, three-necked, round-bottomed flask is fitted with a mechanical stirrer, pressure-equalizing dropping funnel, and a thermometer. The flask is charged with 44.05 g (0.50 mol) of (S)-(-)-2-methyl-1-butanol (Note 1), 0.78 g (5 mmol) of 2,2,6,6-tetramethylpiperidin-1-oxyl (Note 2), 170 mL of dichloromethane, and a solution of 5.95 g (0.050 mol) of potassium bromide in 25 mL of water (Note 3). The reaction mixture is vigorously stirred and cooled to -10°C with a salt-ice bath, then 550 mL (0.55 mol) of 1 M aqueous sodium hypochlorite (Note 4) at pH 9.5 (Note 5) is added over 15-20 min (Note 6), keeping the temperature of the reaction mixture between 10 and 15°C . The mixture is stirred a further 3 min (Note 7). The orange organic phase is separated and the aqueous phase (Note 8) is extracted with 50 mL of dichloromethane. The combined organic extracts are washed with 100 mL of 10% aqueous hydrochloric acid containing 1.6 g (0.010 mol) of potassium iodide (Note 9), 60 mL of 10% aqueous sodium thiosulfate (Note 10) and 60 mL of water (Note 11).

The organic phase is dried over anhydrous magnesium sulfate and then distilled at atmospheric pressure through a 20-cm Vigreux distilling column to give 35.3 - 36.3 g (82-84%) (Note 12) of (S)-(+)-2-methylbutanal as a colorless oil, bp 90-92°C (GC purity > 99%) (Note 13), $[\alpha]_D^{22} +36.8^\circ$ (acetone, c 2.5) (Notes 14, 15, and 16).

2. Notes

1. (S)-(-)-2-Methyl-1-butanol (GC purity > 99.5%; $[\alpha]_D^{20} -6.6 \pm 0.3^\circ$ (ethanol, c 10) was purchased from Fluka Chemie AG. Esterification with (R)-(+)-3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid (Mosher's acid)² and subsequent ¹H and ¹⁹F NMR analyses at 300 MHz of the resulting ester showed an enantiomeric purity of (S)-(-)-2-methyl-1-butanol > 99%.

2. 2,2,6,6-Tetramethylpiperidin-1-oxyl from Nacalai Tesque, Inc., Kyoto, Japan, also available from Janssen Chimica, Beerse, Belgium, was used. 4-Methoxy-2,2,6,6-tetramethylpiperidin-1-oxyl, prepared according to the procedure of Endo,³ can also be used.⁴

3. In the absence of potassium bromide longer reaction times are required.⁴

4. Concentrations of aqueous sodium hypochlorite in the range 0.3-2.0 M have been used successfully.

5. The pH (~12.7) of fresh commercial 1 M aqueous sodium hypochlorite is adjusted to 9.5 by dissolving 17 g of sodium hydrogen carbonate per liter immediately before use.

6. If the reaction is carried out on a 1-10 mmol scale, the temperature is easily maintained at 0°C and the reaction is over in a few minutes.⁴ On a larger scale, a very efficient cooling system is required to maintain the temperature at about 0°C. When conventional laboratory equipment is used, the conditions described in this procedure

are a reasonable compromise between two requirements: i) fast addition of the aqueous sodium hypochlorite, and ii) temperature in the reaction medium low enough to minimize the catalyst decomposition.⁴ Longer reaction times increase slightly the formation of 2-methylbutanoic acid.

7. At this stage the reaction can be monitored by GC: 1 m by 3 mm OV 101 5% on Chromosorb HP 100-120 mesh column, 50°C (2 min), then 50°C to 90°C (15°C per min).

8. (S)-(+)-2-Methylbutanoic acid, $[\alpha]_D^{20} +18.7^\circ$ (ethanol, c 1.1) (lit.⁵ $[\alpha]_D^{22} +16.3^\circ$, ethanol, c 1.1) (1.5-2.6 g, 3-5% yield) can be isolated by acidic work up of the aqueous phase.

9. Washing with hydrochloric acid and potassium iodide removes 2,2,6,6-tetramethylpiperidin-1-oxyl from the organic phase.⁶ Because of its volatility, the catalyst cannot be eliminated in the distillation of crude aldehyde.

10. Washing with 10% aqueous sodium thiosulfate leads to a colorless organic phase, indicating total elimination of the catalyst.

11. The aqueous phase must be neutral. Acidic impurities catalyze trimerization of the anhydrous aldehyde⁷ in the distillation stage.

12. Yields can be further increased with a more efficient separation of the (S)-(+)-2-methyl-1-butanal contained in the top fractions.

13. The spectral properties of (S)-(+)-2-methylbutanal are as follows: IR (film) cm^{-1} : 2970, 2940, 2890, 2820, 2710, 1725, 1460; ^1H NMR (300 MHz, CDCl_3) δ : 0.94 (t, 3 H), 1.09 (d, 3 H), 1.33-1.54 (m, 1 H), 1.64-1.85 (m, 1 H), 2.18-2.33 (m, 1 H), 9.63 (d, 1 H).

14. Reduction with borane/tetrahydrofuran⁸ regenerated enantiomerically pure (S)-(-)-2-methyl-1-butanol, as shown by esterification with Mosher's acid and subsequent NMR analysis of the ester (see Note 1).

15. When practical (S)-(-)-2-methyl-1-butanol (GC purity 95%; $[\alpha]_D^{20} -6.3 \pm 0.5^\circ$ (EtOH, c 10) from Fluka Chemie was used, (S)-(+)-2-methylbutanal having $[\alpha]_D^{20} +33.1^\circ$ (acetone, c 2.5) was obtained.

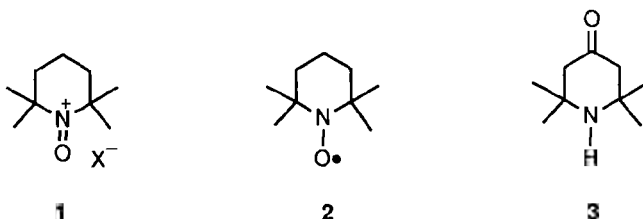
16. Oxidation of (S)-(-)-2-methyl-1-butanol to (S)-(+)-2-methylbutanal has been previously carried out in low yields by chromium oxidation,⁹ under phase transfer catalysis,¹⁰ or by Swern oxidation in the presence of tributylamine.¹¹

3. Discussion

Oxammonium salts **1** have been used extensively either in stoichiometric or in catalytic amounts¹² for the oxidation of primary and secondary alcohols to the corresponding carbonyl derivatives.

The catalytic procedure described here allows a fast, cheap and highly selective conversion of primary alcohols into aldehydes, using sodium hypochlorite as the oxidant in a two-phase (dichloromethane-water) system. Aqueous sodium hypochlorite is buffered at pH 8.6-9.5 to ensure the presence of hypochlorous acid in the organic layer.¹³

Oxammonium salt **1**, the effective oxidant species, is continuously generated from nitroxyl radical **2** by hypochlorous acid in the organic phase. Radical **2** is one of

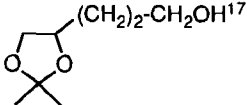
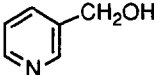


the most stable radicals known, and is easily prepared from the inexpensive triacetoneamine **3**.¹⁴ The oxidation is very exothermic; for this reason scale up of the reaction needs a very efficient cooling system to maintain the temperature in the optimum 0-15°C range. One one-hundredth (0.01) molar equivalent of nitroxyl radical **2** is generally used, but on this reaction scale the amount of catalyst can be reduced to 0.002 molar equivalent, without substantially affecting the reaction time. Sodium hypochlorite is used in only slight excess and is entirely consumed, an unusual occurrence for reactions carried out under aqueous, organic two-phase conditions.¹⁵

Conversion of saturated, primary alkyl and aryl alkyl alcohols into the corresponding aldehydes can be achieved by this method provided that the alcohols are entirely dissolved in the organic phase. Relatively unstable protective groups are not affected, as in the oxidation of the acetonide of 1,2,6-hexanetriol, whereas conjugated and isolated double bonds give rise to side reactions which considerably decrease selectivities and yields.⁴ Some examples of aldehydes synthesized with this method are reported in Table 1. Under the same conditions, secondary alcohols are oxidized to ketones. Addition of catalytic amounts of quaternary onium salts allows fast and total conversion of primary alcohols and aldehydes into carboxylic acids making this methodology very versatile.⁴

When the limitations outlined above are considered, the procedure described here appears to be easier and cheaper than most methods in the condensed phase known to date.¹⁶ Furthermore, alkali halides are almost the only contaminants in the waste water, making the scale up of this method very attractive.

TABLE I
OXIDATION OF PRIMARY ALCOHOLS TO ALDEHYDES

Alcohol	Isolated Yield (%)
1-Heptanol	88
1-Octanol	92
1-Nonanol	92 ⁴
1-Undecanol	93 ⁴
	85
Benzyl alcohol	90 ⁴
p-Nitrobenzyl alcohol	89
m-Nitrobenzyl alcohol	88
	75

1. Centro CNR and Dipartimento di Chimica Organica e Industriale dell'Università, Via Golgi 19, I-20133 Milano, Italy.
2. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
3. Miyazawa, T.; Endo, T.; Shiihashi, S.; Okawara, M. *J. Org. Chem.* **1985**, *50*, 1332.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

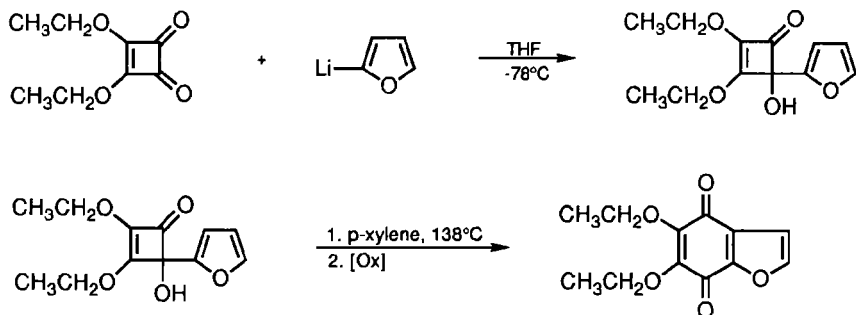
(S)-(+)-2-Methylbutanal: Butyraldehyde, 2-methyl-, (S)-(+)- (8); Butanal, 2-methyl-, (S)-(9); (1730-97-8)

(S)-(-)-2-Methyl-1-butanol: 1-Butanol, 2-methyl-, (S)-(-)- (8); 1-Butanol, 2-methyl-, (S)-(9); (1565-80-6)

Tetramethylpiperidin-1-oxyl: 1-Piperidinyloxy, 2,2,6,6-tetramethyl- (9); (2564-83-2)

4-Methoxy-2,2,6,6-tetramethylpiperidin-1-oxyl: 1-Piperidinyloxy, 4-methoxy-2,2,6,6-tetramethyl (11); (95407-69-5)

REARRANGEMENT OF 4-ARYL-4-HYDROXY-2,3-DIALKOXYCYCLOBUTENEDIONES TO ANNULATED HYDROQUINONES AND QUINONES: 5,6-DIETHOXYBENZOFURAN-4,7-DIONE



Submitted by S. T. Perri, P. Rice, and H. W. Moore.¹

Checked by Ho-Jung Kang and Leo A. Paquette.

1. Procedure

A 500-mL, round-bottomed flask is flame-dried and flushed with nitrogen. The flask is equipped with a magnetic stirring bar and a rubber septum and charged with 4.14 g (60.9 mmol) of furan (Note 1) and 300 mL of dry tetrahydrofuran (Note 2). The solution is stirred and cooled in an ethylene glycol-dry ice bath (-15°C) and 24.17 mL (55.6 mmol) of 2.3 M butyllithium is added slowly by means of a syringe pump (rate = 1.5 mL/min). After complete addition, the solution is stirred an additional 30 min. The ethylene glycol-dry ice bath is replaced with an ice bath and the solution stirred for 1.5 hr at 0°C . The flask is then cooled to -78°C in a dry ice-acetone bath.

A 1000-mL, round-bottomed flask is flame-dried and flushed with nitrogen. The flask is equipped with a magnetic stirring bar and a rubber septum and charged with

9.00 g (52.9 mmol) of diethyl squarate (Note 3) and 450 mL of dry tetrahydrofuran (Note 2). The solution is stirred and cooled in a dry ice-acetone bath at -78°C . The solution of 2-lithiofuran is transferred dropwise via cannula to the flask containing the diethyl squarate which is stirred rapidly. After complete addition (45 min), the solution is stirred for 20 min and quenched by pouring the cold solution into a separatory funnel containing 150 mL of aqueous 10% ammonium chloride and 100 mL of diethyl ether. The separatory funnel is shaken vigorously until phase separation is achieved and all of the ice has melted. The aqueous phase is separated from the organic phase and the aqueous layer is extracted twice with 40-mL portions of diethyl ether. The combined organic layer is washed with 125 mL of brine solution and dried over solid anhydrous potassium carbonate (Note 4) for 5 min with gentle swirling.

The solution is decanted from the potassium carbonate (Note 5) and concentrated on a rotary evaporator (bath temperature = $23\text{--}40^{\circ}\text{C}$) to approximately 150 mL in a 1000-mL round-bottomed flask. Then 400 mL of dry p-xylene (Note 6) is added and the flask is placed on the rotary evaporator at a bath temperature of 40°C to remove the remaining tetrahydrofuran and diethyl ether. The flask containing the remaining p-xylene solution of the cyclobutenone is fitted with a reflux condenser and heated at reflux for 3 hr under nitrogen. The flask is cooled to ambient temperature and the solvent is removed on a rotary evaporator fitted with a bump trap at a bath temperature of 70°C to give a red oil.

The oil is dissolved in 500 mL of diethyl ether and washed with three 200-mL portions of an ethanolic ferric chloride solution (Note 7). The aqueous layers are separated from the organic phase and extracted with four 100-mL portions of diethyl ether. The combined organic layer is washed with saturated sodium bicarbonate solution (Note 8) until the aqueous wash is no longer acidic. The resulting neutralized aqueous extracts are combined and extracted with three 30-mL portions of diethyl ether. The organic extracts are combined, washed with 150 mL of brine solution and

dried over magnesium sulfate. The solution is filtered and concentrated on a rotary evaporator to give the quinone as a red solid. The solid is recrystallized from methanol to yield 10.4-10.5 g of the quinone as orange needles in 2-3 crops (83-84% based on diethyl squarate), mp 54-55°C (Note 9).

2. Notes

1. Furan was purchased from Aldrich Chemical Company, Inc., and used as such.

2. Tetrahydrofuran was distilled under argon from benzophenone ketyl.

3. 3,4-Diethoxy-3-cyclobutene-1,2-dione is commercially available from Aldrich Chemical Company, Inc. *Caution: This substance was found to cause severe skin rashes, and extreme care should be exercised in handling it.* The dimethoxy analog appears to be safer. Diethyl squarate has the following spectral properties: IR (neat) cm^{-1} : 1830, 1741, and 1609; ^1H NMR (CDCl_3 , 300 MHz) δ : 1.47 (t, 6 H, $J = 2.9$), 4.47 (q, 4 H, $J = 7.1$).

4. Prolonged drying of the cyclobutenone over potassium carbonate resulted in product decomposition. Anhydrous magnesium sulfate was found to hydrolyze the product during the thermolysis step.

5. The cyclobutenone was pure enough to use in the next step without purification. This compound is stable for a few hours in solution while kept cold ($<5^\circ\text{C}$) and anhydrous.

6. Certified p-xylene was purchased from Fisher Scientific Company and used as such.

7. Ferric chloride was purchased from Mallinckrodt, Inc. A saturated solution of 80 g of ferric chloride in 500 mL of water was diluted with 500 mL of ethanol, filtered, and used as such. The oxidation could be followed by TLC using Engel stain.

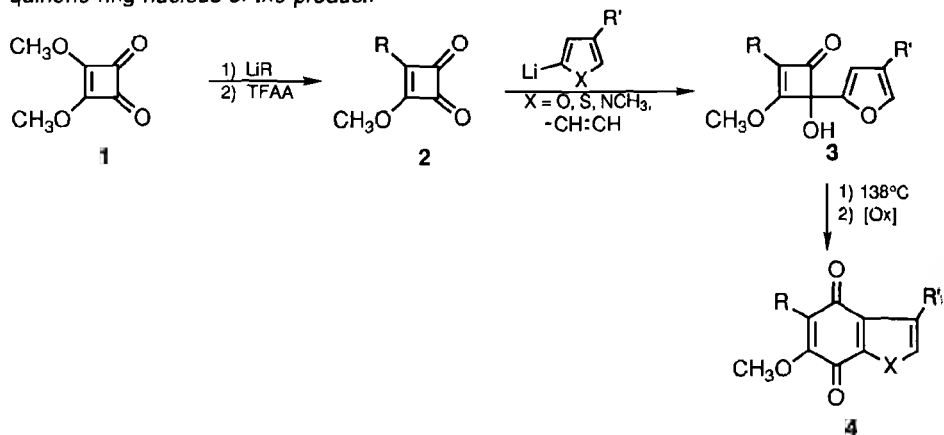
8. Quinones are generally sensitive to bases and some decomposition may occur if the product is exposed for a prolonged period of time to sodium bicarbonate. Therefore the neutralization wash was carried out quickly.

9. The spectral properties of the product are as follows: IR (CHCl_3) cm^{-1} : 2980, 1667, 1480, 1370, 1290, 1250, and 1179; ^1H NMR (CDCl_3 , 500 MHz) δ : 1.42 (2 overlapping t, 6 H, two CH_3), 4.30 (2 overlapping q, 4 H, two CH_2), 6.81 (d, 1 H, $J = 1.9$), 7.67 (d, 1 H, $J = 1.8$); ^{13}C NMR (CDCl_3) δ : 15.7, 15.8, 70.2, 70.3, 108.3, 126.7, 145.7, 146.6, 148.5, 150.1, 172.7, 178.8; EI-MS (70 EV): $m/z = 236$ (19%), 208 (21), 193 (8), 180 (24), 163 (7), 152 (100), 123 (9).

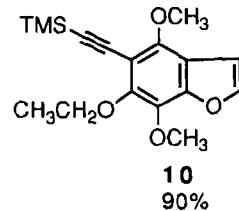
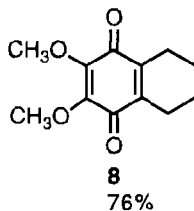
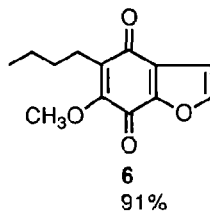
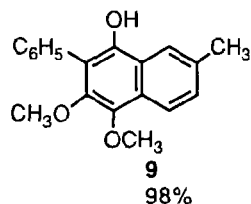
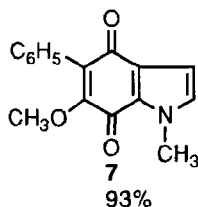
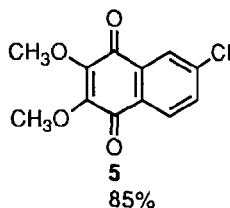
3. Discussion

This procedure describes a synthetic route to annulated hydroquinones/quinones. The example represents a general, convergent, regiospecific and usually high yielding method. This is further elaborated by the generalized scheme given below. Specifically, dialkoxycyclobutenediones, e.g., dimethyl squarate, **1**, are easily converted to unsymmetrical cyclobutenediones **2** upon treatment with an organolithium reagent ($\text{R}=\text{alkyl, aryl, alkenyl, alkynyl}$, -78°C , THF) followed by treatment with trifluoroacetic anhydride (-78°C , TFAA) and an aqueous work-up.^{2,3,4} Treatment of **2** with an aryllithium reagent results in the regiospecific formation of the cyclobutenones **3** via 1,2-addition to the more nucleophilic carbonyl group. These adducts then undergo facile rearrangement to the corresponding annulated hydroquinones in refluxing *p*-xylene. The product is usually isolated as the quinone **4** after an oxidative work-up.^{5,6,7} It is noted that alkenyl lithium reagents as well as alkynyl analogs also add regiospecifically to the cyclobutenediones **2** to give the corresponding cyclobutenones. The alkenyl adducts, like the aryl analogs, also rearrange to the corresponding hydroquinones. The alkynyl

adducts rearrange directly to the corresponding quinones via a unique pathway involving migration of the alcoholic proton of the 4-hydroxycyclobutenone to the quinone ring nucleus of the product.^{8,9}



Compounds **5-10** are specific examples of annulated products which have been prepared by the method outlined here.



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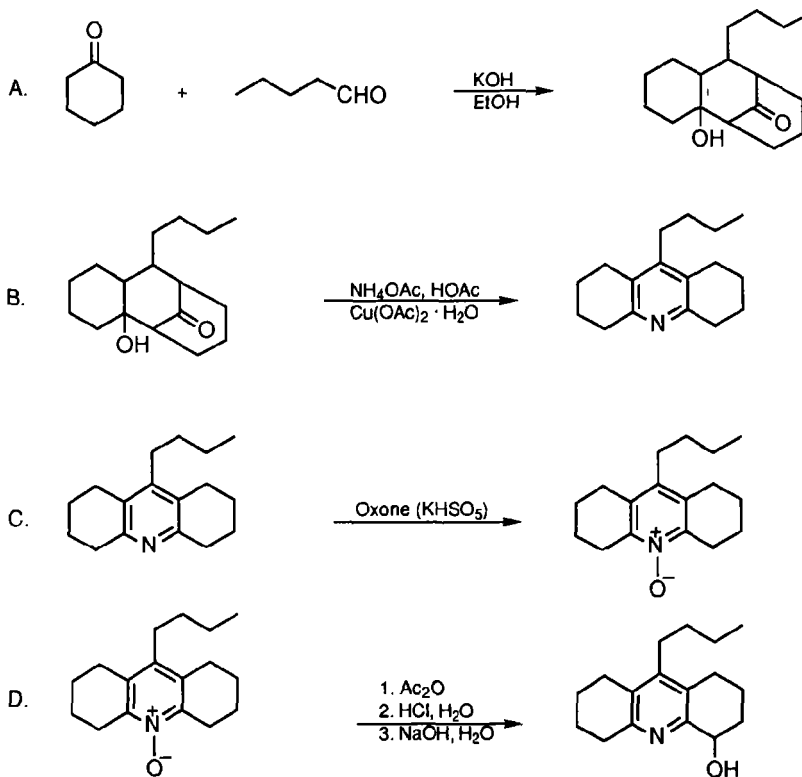
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Furan (8,9); (110-00-9)

Diethyl squarate: Cyclobutenedione, diethoxy- (8); 3-Cyclobutene-1,2-dione,
3,4-diethoxy- (9); (5231-87-8)

9-n-BUTYL-1,2,3,4,5,6,7,8-OCTAHYDROACRIDIN-4-OL
(4-Acridinol; 9-butyl-1,2,3,4,5,6,7,8-octahydro-)



Submitted by Thomas W. Bell, Young-Moon Cho, Albert Firestone, Karin Healy,
 Jia Liu, Richard Ludwig and Scott D. Rothenberger.¹
 Checked by Edward R. Holler, Jr. and Bruce E. Smart .

1. Procedure

A. *8-n-Butyl-2-hydroxytricyclo[7.3.1.0^{2,7}]tridecan-13-one*. A 2-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, thermometer, 500-mL pressure equalizing dropping funnel, and a reflux condenser fitted with a nitrogen gas inlet tube which is attached to a mineral oil bubbler. The flask is flushed with nitrogen and then charged with 1.0 L (947 g, 9.65 mol) of cyclohexanone (Note 1). The cyclohexanone is stirred and heated to 70-75°C under nitrogen, a solution of 9.0 g (0.14 mol) of potassium hydroxide (Note 2) in 85 mL of absolute ethanol is added in one portion, and then a solution of 150 mL (122 g, 1.4 mol) of pentanal (Note 3) in 140 mL of absolute ethanol is added dropwise over a period of 8 hr while maintaining the reaction mixture at 70-75°C. The reaction mixture is stirred and held at 70-75°C for an additional 12 hr, and then allowed to cool to room temperature. The reaction flask is immersed in an ice bath, the inner wall of the flask is scratched with a glass rod to initiate crystallization, and the mixture is kept at 0°C for 4 hr to complete the crystallization. The colorless crude product is collected by vacuum filtration and washed with 200 mL of cold ether. The filtrates are combined and concentrated to approximately 200 mL with a rotary evaporator. The precipitated white solid is collected by filtration and washed with water (2 x 200 mL) and 200 mL of cold ether to give a second crop of crude product. The two crops are combined and recrystallized from 750 mL of methanol, washed with water, and dried at 60°C under vacuum (1 mm) to give 228-230 g (61-62%) of 8-n-butyl-2-hydroxytricyclo[7.3.1.0^{2,7}]tridecan-13-one, mp 140-141°C (Note 4).

B. *9-n-Butyl-1,2,3,4,5,6,7,8-octahydroacridine*. A 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, glass stopper, and a reflux condenser fitted with a nitrogen gas inlet tube which is attached to a mineral oil bubbler is flushed with nitrogen and then charged with 17.0 g (0.22 mol) of ammonium

acetate, 82 g (0.41 mol) of cupric acetate monohydrate (Note 5), and 200 mL of glacial acetic acid. The mixture is stirred and heated at reflux for 15 min under a static atmosphere of nitrogen. The resulting solution is allowed to cool below reflux and 53 g (0.20 mol) of 8-n-butyl-2-hydroxytricyclo[7.3.1.0^{2,7}]tridecan-13-one is added in several portions. The blue-green reaction mixture is then refluxed under nitrogen for 3 hr with efficient stirring to control foaming. The mixture is allowed to cool to room temperature and then chilled in an ice bath for 3 hr. The precipitated cuprous acetate is collected by vacuum filtration using a fritted glass funnel (medium porosity) and washed with 100 mL of acetic acid. The combined filtrates are diluted with 500 mL of water, cooled in an ice bath, and carefully neutralized by slowly adding 33.3% (w/w) aqueous sodium hydroxide (Note 6). The resulting cloudy mixture is transferred to a separatory funnel and extracted with ether (400 mL, then 2 x 200 mL). The combined ether extracts are washed successively with 140 mL of 3% aqueous sodium hydroxide and 70 mL of saturated aqueous sodium chloride, and then dried over anhydrous magnesium sulfate along with 1 g of decolorizing charcoal (Norit). The solids are removed by filtration and washed with 200 mL of ether. The combined filtrates are concentrated to minimum volume with a rotary evaporator, and the residual solid is dried to a constant weight under vacuum (1 mm) to give 44.3-47.0 g (91-96%) of beige, crystalline product, mp 36-38°C. The product is further purified by adding a solution of 44.3 g of material in 90 mL of dichloromethane to a column of Woelm neutral alumina (75 x 28 mm), and eluting with an additional 300 mL of dichloromethane. The solvent is removed on a rotary evaporator to give 42.1 g (86%) of white crystalline solid, mp 41-43°C (Note 7).

C. 9-n-Butyl-1,2,3,4,5,6,7,8-octahydroacridine N-oxide. A 2-L, round-bottomed flask equipped with a magnetic stirrer and a reflux condenser fitted with a nitrogen inlet tube is flushed with nitrogen and charged with 790 mL of methanol, 240 mL of water, 38.0 g (0.16 mol) of purified 9-n-butyl-1,2,3,4,5,6,7,8-octahydroacridine, 28.5 g (0.34

mol) of sodium bicarbonate, and 72.0 g (0.12 mol) of Oxone® (Note 8). The suspension is stirred under nitrogen at 45-50°C for 24 hr (Note 9). The mixture is cooled to room temperature, filtered, and the filtercake is washed with methanol (2 x 50 mL). The methanol is removed from the combined filtrates with a rotary evaporator, and the resulting mixture is extracted with dichloromethane (3 x 100 mL). The combined extracts are washed with water (2 x 50 mL) and dried over magnesium sulfate. The drying agent is removed by filtration, the filtrate is concentrated with a rotary evaporator, and the residual solid is dried under vacuum (0.1-0.5 mm) to give 40.0 g (99%) of 9-n-butyl-1,2,3,4,5,6,7,8-octahydroacridine N-oxide as a cream colored solid, mp 92-94°C (Notes 10, 11, and 12).

D. 9-n-Butyl-1,2,3,4,5,6,7,8-octahydroacridin-4-ol. Crude 9-n-butyl-1,2,3,4,5,6,7,8-octahydroacridine N-oxide (38.9 g, 0.15 mol) is placed in a 1-L, three-necked, round-bottomed flask equipped with a magnetic stirrer, glass stopper, and a reflux condenser fitted with a nitrogen inlet tube, and a 500-mL addition funnel. Acetic anhydride (300 mL) is placed in the addition funnel, deaerated by sparging with helium for 30 min, and then added rapidly to the nitrogen-purged reaction flask. The reaction mixture is stirred and heated in a 100-110°C oil bath for 2 hr. The reflux condenser is replaced by a simple distillation head and approximately 280 mL of acetic anhydride is removed by distillation at water-aspirator pressure (25-35 mm). To the brown residue is added 470 mL of 3 M aqueous hydrochloric acid, and the resulting mixture is refluxed under nitrogen for 1.5 hr. The mixture is allowed to cool to room temperature, chilled in an ice bath, and made alkaline (pH 12-13) by slowly adding about 550 mL of cold 4 M aqueous sodium hydroxide. The resulting cloudy mixture is extracted with chloroform (3 x 150 mL) and the combined extracts are dried over anhydrous sodium sulfate. The drying agent is removed by filtration and the filtrate is concentrated to dryness with a rotary evaporator. The brown residue is recrystallized from 75 mL of ethyl acetate, and the collected product is recrystallized

again from 50 mL of ethyl acetate (Note 13) to give 25.9 g (67%) of 9-n-butyl-1,2,3,4,5,6,7,8-octahydroacridin-4-ol as a light beige solid, mp 107-109°C (Note 14).

2. Notes

1. Cyclohexanone (99.8%) was obtained from Aldrich Chemical Company, Inc. and was used without purification.

2. Certified grade potassium hydroxide (86.6%) from Fisher Scientific was used.

3. Pentanal (99%) was obtained from Aldrich Chemical Company, Inc., redistilled under a static atmosphere of nitrogen (bp 103°C), and used immediately.

4. The product has the following spectroscopic properties: ^1H NMR (300 MHz, CDCl_3) δ : 0.89 (t, 3 H, $J = 6$, CH_3), 1.1-2.3 (m, 23 H, CH_2 , CH), 2.44 (m, 1 H, CH_2), 2.72 (s, 1 H, OH); IR (KBr) cm^{-1} : 3413 (s), 2931 (s), 2857 (s), 1703 (s), 1455 (m), 1406 (m), 1378 (m), 1352 (m), 1285 (m), 1267 (m), 1206 (m), 1140 (m), 968 (m), 931 (m); mass spectrum m/z (relative abundance, 70 eV): 264 (M^+ , 10), 167 (85), 166 (100). The submitters report that a second recrystallization gives analytically pure material, mp 141-142°C. Anal. Calcd for $\text{C}_{17}\text{H}_{28}\text{O}_2$: C, 77.22; H, 10.67. Found: C, 77.34; H, 10.51.

5. Ammonium acetate (99+%) and copper(II) acetate monohydrate (98+%) were obtained from Aldrich Chemical Company, Inc.

6. Approximately 470 mL of sodium hydroxide was required to reach a final pH of 8-9. A lower pH leads to extraction of acetic acid, whereas higher pH (10) causes the formation of a white precipitate that makes a phase separation difficult during extraction.

7. The product is pure by thin-layer chromatographic analysis (Alumina GF Uniplate from Analtec, Inc., 1:1 ethyl acetate:hexane solvent, $R_f = 0.79$) and ^1H NMR

analysis. The product has the following spectroscopic properties: ^1H NMR (300 MHz, CDCl_3) δ : 0.96 (t, 3 H, $J = 6$, CH_3), 1.42 (m, 4 H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.7-1.9 (m, 8 H, H2, H3, H6, H7), 2.49 (m, 2 H, ArCH_2), 2.68 (m, 4 H, ArCH_2), 2.85 (m, 4 H, ArCH_2); IR (neat) cm^{-1} : 2932 (s), 2858 (s), 1565 (m), 1438 (m), 1409 (m), 1246 (w); mass spectrum, m/z (relative abundance 70, eV): 243 (M^+ , 51), 228 (6), 214 (16), 201 (64), 200 (56), 186 (100). The submitters obtained an analytically pure sample by bulb-to-bulb distillation of the initial beige product. Anal. Calcd for $\text{C}_{17}\text{H}_{25}\text{N}$: C, 83.89; H, 10.35; N, 5.75. Found: C, 83.58; H, 10.07; N, 5.40.

8. Oxone®, the Du Pont Company trade name for potassium peroxymonosulfate, has the composition $2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$, and was purchased from Aldrich Chemical Company, Inc.

9. Oxidation may be monitored by thin-layer chromatography (Alumina GF Uniplat, 1:1 ethyl acetate:hexane). The R_f values of the N-oxide product and starting material are 0.30 and 0.79 respectively (Note 7).

10. The submitters report obtaining 39 g (96%) of pale yellow product, mp 89-92°C, when the beige starting material from Part B, mp 36-39°C, was used without further purification. The checkers, however, obtained only an 80% yield of N-oxide, mp 87-91°C, when crude starting material was used.

11. The product is sufficiently pure to be used directly in Part D, but may be further purified by recrystallization from ethyl acetate:hexane (1:6) to give colorless material, mp 99-101°C. The product has the following spectral properties: ^1H NMR (300 MHz, CDCl_3) δ : 0.97 (t, 3 H, $J = 6$, CH_3), 1.42 (m, 4 H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.7-1.9 (m, 8 H, H2, H3, H6, H7), 2.53 (m, 2 H, ArCH_2), 2.69 (m, 4 H, H1, H8), 2.97 (m, 4 H, H4, H5); IR (KBr) cm^{-1} : 2942 (s), 2857 (s), 1477 (m), 1444 (m), 1424 (m), 1398 (m), 1350 (m), 1322 (m), 1286 (s), 1236 (m), 1096 (s).

12. The submitters provided the following alternative procedure for conducting the oxidation with m-chloroperoxybenzoic acid (MCPBA) in place of Oxone®: Into a 1-

L, round-bottomed flask equipped with a magnetic stirrer, reflux condenser, and a 250-mL addition funnel are placed 56.3 g (0.26 mol) of MCPBA (80%) and 350 mL of dichloromethane. The suspension is stirred and a solution of 38.0 g (0.16 mol) of 9-n-butyl-1,2,3,4,5,6,7,8-octahydroacridine in 120 mL of dichloromethane is added rapidly (exotherm). When the reaction mixture ceases to boil gently from the heat of reaction, it is heated to extend the reflux period to a total of 2.5 hr. The reaction mixture is cooled to room temperature, extracted with 0.5 M aqueous sodium hydroxide (4 x 450 mL), and dried over anhydrous sodium sulfate. The drying agent is removed by filtration, the filtrate is concentrated with a rotary evaporator, and the residual solvent is removed at 0.1 mm pressure to afford 40 g (99%) of yellow crystalline product, mp 96-100°C.

13. For both recrystallizations, the solid is taken up in boiling ethyl acetate, rapidly filtered, and the filtrate is allowed to cool slowly to room temperature. It then is stored at -5°C overnight in a refrigerator prior to collecting the crystals.

14. The product ($R_f = 0.47$) contains a trace of 9-n-butyl-1,2,3,4,5,6,7,8-octahydroacridine ($R_f = 0.79$) by thin-layer chromatographic analysis (Alumina GF Uniplate, 1:1 ethyl acetate:hexane). The checkers chromatographed a 10-g sample on a Woelm neutral alumina column (75 x 28 mm) using 300 mL of warm ethyl acetate as eluent to give 9.2 g of colorless product, mp 107-109°C. The original and chromatographed products have identical spectroscopic properties: ^1NMR (300 MHz, CDCl_3) δ : 0.96 (t, 3 H, $J = 7$, CH_3), 1.41 (m, 4 H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.7-1.9 (m, 6 H, H_2 , H_6 , H_7), 2.03 (m, 1 H, H_3), 2.27 (m, 1 H, H_3), 2.50 (m, 2 H, 9- CH_2), 2.70 (m, 4 H, H_1 , H_8), 2.84 (m, 2 H, H_5), 4.63 (m, 1 H, H_4), 4.76 (s, 1 H, OH); IR (KBr) cm^{-1} : 3174 (s, br), 2942 (s), 2713 (m), 1569 (s), 1432 (s), 1407 (s), 1377 (m), 1338 (s), 1307 (s), 1253 (m), 1216 (m), 1169 (m), 1155 (s), 1094 (s), 1081 (s), 1005 (s), 962 (s), 939 (m), 893 (m). The submitters obtained an analytical sample, mp 104-105°C, by recrystallization from

ethyl acetate and drying for 6 hr at room temperature (0.1 mm). Anal. Calcd for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.81, H, 9.53, N, 5.19.

3. Discussion

Taken together, Steps A and B of this procedure describe the most expedient, large scale approach to 9-n-butyl-1,2,3,4,5,6,7,8-octahydroacridine, which is prepared in about 60% overall yield from inexpensive starting materials. This heterocycle is an important building block for "hexagonal lattice" receptors, which are relatively rigid, planar hosts for metal ions and organic molecules.²

Several methods exist for preparing pyridines that are annelated to nonaromatic rings in the [b,e] positions,³⁻⁶ but most do not also introduce an alkyl group in the 4-position. n-Butyl groups are found to lend solubility to higher molecular weight hexagonal lattice receptors. Step A of this procedure is a modification of the method of Tilichenko, who has reported the condensation of cyclohexanone with various aldehydes.⁷ The reaction involves the following sequence: aldol condensation to form 2-pentylidenecyclohexanone, Michael addition of cyclohexanone enolate, and intramolecular aldol condensation of the resulting 1,5-diketone. Many aldol products are formed and the yield of keto alcohol depends strongly on: 1) reaction temperature; 2) use of a large excess of cyclohexanone; and 3) prolonged addition of the aldehyde. The ease of product isolation is particularly dependent on its crystallinity and solubility.

If a substituent is not required in the 4-position of the new pyridine ring, then viable alternatives to the current procedure include trimethylhydrazonium-salt pyrolysis⁵ and various methods for condensing ketones or enamines with formaldehyde or methyleneammonium salts.^{4a,f,6d} The latter methods often involve isolation of the intermediate 1,5-diketone, which is condensed with ammonia or

ammonium salts to form the pyridine ring,^{4b-d,f} The yield of this cyclization is limited by disproportionation of the intermediate dihydropyridine.⁸ Hydrazine^{4e} or hydroxylamine^{2a,4a} may also be used, but yields are similar to those obtained with ammonium acetate in acetic acid. The cupric acetate/ammonium acetate method described in Step B nearly quantitatively gives annelated pyridines from various 1,5-diketone equivalents.⁸ Cupric acetate appears to be the oxidant of choice for intercepting dihydropyridines before disproportionation can occur.

Step C describes a method for oxidizing a pyridine to its N-oxide with Oxone® (potassium hydrogen persulfate). The more traditional oxidant, m-chloroperoxybenzoic acid (MCPBA), works equally well, but the availability of 80-85% pure MCPBA is now limited. Pyridine N-oxides may also be prepared with hydrogen peroxide in acetic acid,^{9,10} but reaction time is variable and removal of acetic acid is inconvenient for large scale preparations. Potassium hydrogen persulfate (Oxone®) is an inexpensive alternative to MCPBA in many oxidation reactions.¹¹ The oxidation procedure given here avoids the formation of volatile peroxides, which occurs in ketone-catalyzed N-oxidation of pyridine by persulfate.^{11b,e} A 50% excess of Oxone® is used, assuming 100% activity. The submitters used Oxone® of 67-68% purity by iodometric titration. Less oxidant leads to incomplete reaction or inconveniently long reaction times.

Synthesis of annelated polypyridines or hexagonal lattice receptors from 1,2,3,4,5,6,7,8-octahydroacridines requires oxidative functionalization of the 4-position (CH₂ group bonded to the pyridine 2-position). In Step D this is accomplished by "Katada" or "Boekelheide" rearrangement of the N-oxide. This general reaction is commonly used for selective oxidation of alkylated pyridines although the mechanism for conversion of the acetylated N-oxide to the 2-acetoxyalkylpyridine has not been fully elucidated.¹² The current procedure reflects an empirical finding that deoxygenation of the acetic anhydride prior to addition results in slightly higher yields.

Condensation of 2-alkylpyridines with benzaldehyde, followed by ozonolysis of the benzyldene intermediate is a general, alternative route to 2-oxoalkylpyridines.¹³ The N-oxide rearrangement described here is superior when monofunctionalization is required, because condensation of 9-n-butyl-1,2,3,4,5,6,7,8-octahydroacridine with 1 equivalent of benzaldehyde gives a mixture of monobenzyldene and dibenzyldene derivatives.² Recent work by Tilichenko has shown that 1,5-diketones may be converted to monobenzyldene derivatives before forming the pyridine ring,¹⁴ but overall yields are lower than for the current procedure.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

9-n-Butyl-1,2,3,4,5,6,7,8-octahydroacridin-4-ol: 4-Acridinol, 9-butyl-1,2,3,4,5,6,7,8-octahydro- (11); (99922-91-5)

8-n-Butyl-2-hydroxytricyclo[7.3.1.0^{2,7}]tridecan-13-one: 5,9-Methanobenzocycloocten-11-one, 10-butyldodecahydro-4a-hydroxy- (8,9); (24133-22-0)

Cyclohexanone (8,9); (108-94-1)

Pentanal: Valeraldehyde (8); Pentanal (9); (110-62-3)

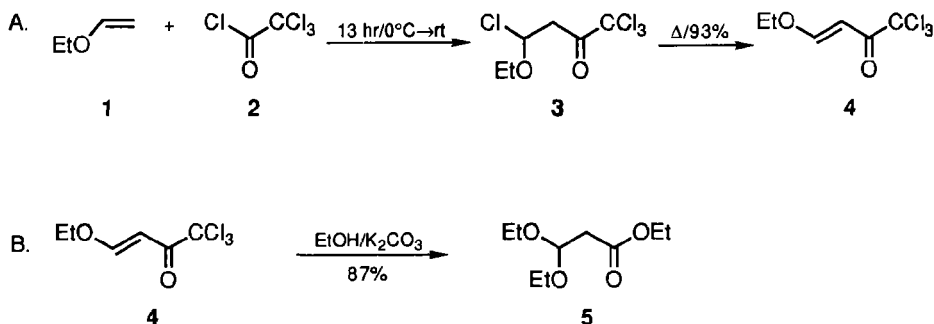
9-n-Butyl-1,2,3,4,5,6,7,8-octahydroacridine: Acridine, 9-butyl-1,2,3,4,5,6,7,8-octahydro- (11); (99922-90-4)

Ammonium acetate: Acetic acid, ammonium salt (8,9); (631-61-8)

Cupric acetate monohydrate: Acetic acid, copper(2+) salt, monohydrate (8,9); (6046-93-1)

Oxone: Peroxymonosulfuric acid, monopotassium salt, mixt. with dipotassium sulfate and potassium hydrogen sulfate (9); (37222-66-5)

**SYNTHESIS OF ALKYL PROPANOATES BY A HALOFORM REACTION OF
A TRICHLORO KETONE: PREPARATION OF ETHYL
3,3-DIETHOXYPROPANOATE
(Propanoic acid, 3,3-diethoxy-, ethyl ester)**



Submitted by L. F. Tietze, E. Voss, and U. Hartfiel.¹

Checked by Daniel Romo and Albert I. Meyers.

1. Procedure

A. *1,1,1-Trichloro-4-ethoxy-3-buten-2-one*, **4**.² A 500-mL, two-necked, round-bottomed flask equipped with a pressure-equalizing addition funnel with drying tube, nitrogen inlet and magnetic stirring bar is charged with trichloroacetyl chloride, **2** (173 g, 0.96 mol) (Note 1). Under nitrogen the flask is cooled with an ice bath to 0°C and ethyl vinyl ether (137 g, 181 mL, 1.90 mol, Note 2) is added within 1 hr to the well-stirred mixture. Stirring is continued for 12 hr allowing the mixture to warm to room temperature without removing the cooling bath (Note 3). The addition funnel is replaced by a short Vigreux column and excess ethyl vinyl ether is removed at 20°C under reduced pressure (20 mm). The bath-temperature is raised (to approx. 140°C)

under reduced pressure (20 mm) to start elimination of hydrogen chloride, which is accompanied by formation of a deep black color and requires 1-2 hr for completion. Distillation of the residue under reduced pressure affords 193 g (92%) of **4**,³ as a bright yellow oil which fades to pale yellow on standing, bp 116-118°C/13 mm, n_D^{24} 1.5129 (Notes 4,5).

B. Ethyl 3,3-diethoxypropanoate, 5. A 500-mL, two-necked, round-bottomed flask equipped with magnetic stirring bar, reflux condenser with drying tube, and 250-mL pressure equalizing addition funnel is charged with dry ethanol (200 mL, 3.4 mol) and anhydrous potassium carbonate (12 g, 87 mmol) and cooled with an ice/water bath. The addition funnel is charged with 1,1,1-trichloro-4-ethoxy-3-buten-2-one, **4** (200 g, 0.92 mol) and the addition is performed with stirring during 30 min. Stirring is continued for 10 hr at room temperature, petroleum ether or pentane (300 mL) is added, and the potassium carbonate is filtered off. After concentration under reduced pressure the residue is distilled through a short Vigreux column, to yield 153 g (87%) of **5**, bp 92-95°C/15 mm, n_D^{24} 1.4117 (Notes 6, 7).

2. Notes

1. Trichloroacetyl chloride (obtained from Fluka Chemical Corporation) was distilled immediately before use.

2. Ethyl vinyl ether (obtained from Fluka Chemical Corporation) was used from a freshly opened bottle containing a stabilizer (0.1% diethylaniline) without purification. The stabilizer seems to be important (see Note 7).

3. An exothermic reaction was observed after removing the ice bath.

4. Distillation should not be performed at a lower pressure.

5. The synthesis of **4** can be carried out on a large scale: a run using 1.8 kg of trichloroacetyl chloride gave **4** in 97% yield. The spectral properties are as follows: IR (neat) cm^{-1} : 2990 (C-H), 1710 (C=O), 1600 (C=C), 835 (C-Cl); ^1H NMR (60 MHz, CDCl_3) δ : 1.38 (t, 3 H, $J = 7$, OCH_2CH_3), 4.08 (q, 2 H, $J = 7$, OCH_2CH_3), 6.13 (d, 1 H, $J = 12.4$, 3-H), 7.87 (d, 1 H, $J = 12.4$, 4-H).

6. Distillation should only be performed at the indicated temperature range. Approximately 20 mL of a dark residue remains after distillation. The spectral properties are as follows: IR (neat) cm^{-1} : 2990, 2940 (C-H), 1740 (C=O), 1115, 1060 (C-O); ^1H NMR (60 MHz, CDCl_3) δ : 1.18 (t, 6 H, $J = 7$, OCH_2CH_3), 1.25 (t, 3 H, $J = 7$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.62 (d, 2 H, $J = 6$, 2-H), 3.30-3.80 (2 AB - systems, 4 H, 2 OCH_2CH_3), 4.13 (q, 2 H, $J = 7$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.93 (t, 1 H, $J = 6$, 3-H).

7. In a similar way, methyl 3,3-dimethoxypropanoate can be prepared using trichloroacetyl chloride and methyl vinyl ether as starting materials. However, in this case, using methyl vinyl ether without a stabilizer, it is necessary to perform the reaction in the presence of pyridine; otherwise extensive polymerization of the vinyl ether takes place.

Procedure: A 1000-mL, three-necked, round-bottomed flask equipped with a pressure-equalizing addition funnel with drying tube, intensive condenser (cryostat temp., -5°C) with nitrogen inlet, and mechanical stirrer, is charged with **2** (270 g, 1.48 mol); pyridine (117 g, 1.48 mol) is added within 15 min under vigorous stirring at room temperature. Under nitrogen, the flask is cooled with an ice bath to -10°C and liquid methyl vinyl ether (112 g, approx. 145 mL, 1.93 mol) is added through a coolable addition funnel (approx. -10°C) within 30 min to the well-stirred mixture. Stirring is continued for 12 hr, allowing the mixture to warm to room temperature without removing the cooling bath. After addition of water (250 mL) and extraction with diethyl ether (2 x 200 mL), the combined organic layers are washed with brine (2 x 50 mL), dried (Na_2SO_4), and the solvent evaporated under reduced pressure. Distillation

(20-cm Vigreux column) of the residue under reduced pressure affords 267 g (88%) of 1,1,1-trichloro-4-methoxy-3-buten-2-one as a colorless liquid, bp 102°C/10 mm, n_D^{20} 1.5238. The spectral properties are as follows: IR (neat) cm^{-1} : 2940, 2840 (C-H), 1710 (C=O), 1600 (C=C); ^1H NMR (60 MHz, CDCl_3) δ : 3.80 (s, 3 H, OCH_3), 6.03 (d, 1 H, $J = 12$, 3-H), 7.77 (d, 1 H, $J = 12$, 4-H). Solvolysis of 1,1,1-trichloro-4-methoxy-3-buten-2-one with methanol to give methyl 3,3-dimethoxypropanoate can be performed according to the procedure given for 5.

3. Discussion

The synthesis of ethyl 3,3-diethoxypropanoate, 5, described here implies acylation of an enol ether followed by a haloform reaction. The procedure is superior to other methods, which afford mixtures of acetals and acrylates,⁴ give only moderate yields,^{5,6,7} require the troublesome use of ketene⁸ or expensive ethyl propiolate,^{9,10,11} need palladium(II) catalysis,¹² or equipment for electrochemical reactions.¹³

Ethyl 3,3-diethoxypropanoate, 5, is the stable, protected derivative of the unstable 3-formylpropanoate. It can be stored at room temperature for several months without decomposition. It is a useful starting material, especially for the synthesis of heterocycles such as coumarins,¹⁴ isoxazoles,¹⁵ pyrimidines,¹⁶ porphyrins,¹⁷ and thiadiazines.¹⁸ Also spermine metabolites,¹⁹ steroids,²⁰ herbicides,²¹ anti-hypertensives,²² photographic sensitizers,²³ cephalosporins,²⁴ lycopodium alkaloids,²⁵ nucleic acids,⁵ and pentaerythritol²⁶ as well as related alcohols can be obtained from 5. Thus ester 5 can be reduced to the corresponding alcohol which yields 3-hydroxypropanal with acidic conditions;²⁶ elimination of ethanol gives 3-ethoxyacrylate.²⁷ Of great interest is also the formylation of 5 to give ethyl 2-formyl-3-oxopropanoate or, starting from methyl 3,3-dimethoxypropanoate, methyl 2-formyl-3-

oxopropanoate.^{10,28} The latter compound has been used in the synthesis of iridoids,²⁸ ipecacuanha alkaloids,²⁹ 1,4-dihydropyridines,²⁹ NADH analogues,³⁰ dihydropyrans,³¹ and branched amino sugars.³²

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Ethyl 3,3-diethoxypropanoate: Propanoic acid, 3,3-diethoxy-, ethyl ester (9);
(10601-80-6).

1,1,1-Trichloro-4-ethoxy-3-buten-2-one: 3-Buten-2-one, 1,1,1-trichloro-4-ethoxy- (11);
(83124-74-7)

Trichloroacetyl chloride: Acetyl chloride, trichloro- (8,9); (76-02-8)

Ethyl vinyl ether: Ether, ethyl vinyl (8); Ethene, ethoxy- (9); (109-92-2)

Methyl 3,3-dimethoxypropanoate: Propanoic acid, 3,3-dimethoxy-, methyl ester (9);
(7424-91-1)

Methyl vinyl ether: Ether, methyl vinyl (8); Ethene, methoxy- (9); (107-25-5)

1,1,1-Trichloro-4-methoxy-3-buten-2-one: 3-Buten-2-one, 1,1,1-trichloro-4-methoxy-,
(E)- (12); (116140-91-1)

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- 2509R Preparation and Diels-Alder Reaction of a Reactive, Electron-Deficient Heterocyclic Azadiene: Dimethyl 1,2,4,5-Tetrazine-3,6-Dicarboxylate. 1,2-Diazine and Pyrrole Introduction. D. L. Boger, J. S. Panek, and M. Patel, Department of Chemistry, Purdue University, West Lafayette, IN 47907
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- 2541* Synthesis of Furans via Rhodium(II) Acetate Catalyzed Reaction of Acetylenes with α -Diazocarbonyls. H. M. L. Davies, W. R. Cantrell, Jr., and J. S. Baum, Department of Chemistry, Wake Forest University, Winston-Salem, NC 27109
- 2542* Nickel-Catalyzed Silylolation of Allylic Dithioacetals: (E,E)-Trimethyl(4-Phenyl-1,3-butadienyl)silane. Z.-J. Ni and T.-Y. Luh, Department of Chemistry, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong
- 2545* α -Acetylenic Esters from α -Acylmethylenephosphoranes: Ethyl 4,4,4-Trifluorotetrolate. B. C. Hamper, Monsanto Agricultural Co., 800 N. Lindburgh Blvd., St. Louis, MO 63167
- 2546* 4-Benzyl-10,19-diethyl-4,10,19-triaza-1,7,13,16-tetraoxacycloheptacosane (Triaza-21-crown-7). K. E. Krakowiak and J. S. Bradshaw, Department of Chemistry, Brigham Young University, Provo, UT 84602
- 2547 Methoxycarbonylmethylation of Aldehydes via Siloxycyclopropanes: Methyl 3,3-Dimethyl-4-oxobutanoate. H.-U. Reissig, I. Reichelt, and T. Kunz, Institut für Organische Chemie, Technische Hochschule Darmstadt, 6100 Darmstadt, Petersenstr. 22, Federal Republic of Germany
- 2548* Tetrahydro-3-benzazepin-2-ones: Lead Tetraacetate Oxidation of Isoquinoline Enamides. G. R. Lenz and R. A. Lessor, Health Care R & D, The BOC Group, Inc., 100 Mountain Ave., Murry Hill, NJ 07974
- 2549* 3,4-Diethylpyrrole and Octaethylporphyrin. J. L. Sessler, A. Mozaffari, and M. R. Johnson, Department of Chemistry, The University of Texas at Austin, Austin, TX 78712-1167
- 2553* 9-Borabicyclo[3.3.1]nonane Dimer. J. A. Soderquist and A. Negron, Department of Chemistry, University of Puerto Rico, Rio Piedras Campus, Rio Piedras, Puerto Rico 00931

- 2555* Iodolactamization: 8-exo-Iodo-2-azabicyclo[3.3.0]octan-3-one.
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The index lists the names of compounds in two forms. The first is the name used commonly in procedures. The second is the systematic name according to **Chemical Abstracts** nomenclature, accompanied by its registry number in parentheses. While the systematic name is indexed separately, it also accompanies the common name. Also included are general terms for classes of compounds, types of reactions, special apparatus, and unfamiliar methods.

Most chemicals used in the procedure will appear in the index as written in the text. There generally will be entries for all starting materials, reagents, intermediates, important by-products, and final products. Entries in capital letters indicate compounds, reactions, or methods appearing in the title of the preparation.

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NOTICE

With Volume 62, the Editors of *Organic Syntheses* began a new presentation and distribution policy to shorten the time between submission and appearance of an accepted procedure. The soft cover edition of this volume is produced by a rapid and inexpensive process, and is sent at no charge to members of the Organic Divisions of the American and French Chemical Society, The Perkin Division of the Royal Society of Chemistry, and The Society of Synthetic Organic Chemistry, Japan. The soft cover edition is intended as the personal copy of the owner and is not for library use. A hard cover edition is published by John Wiley and Sons Inc. in the traditional format, and differs in content primarily in the inclusion of an index. The hard cover edition is intended primarily for library collections and is available for purchase through the publisher. Annual Volumes 60-64 have been incorporated into a new five-year version of the collective volumes of *Organic Syntheses* which has appeared as *Collective Volume Seven* in the traditional hard cover format. It is available for purchase from the publishers. The Editors hope that the new *Collective Volume* series, appearing twice as frequently as the previous decennial volumes, will provide a permanent and timely edition of the procedures for personal and institutional libraries. The Editors welcome comments and suggestions from users concerning the new editions.

NOMENCLATURE

Both common and systematic names of compounds are used throughout this volume, depending on which the Editor-in-Chief felt was more appropriate. The *Chemical Abstracts* indexing name for each title compound, if it differs from the title name, is given as a subtitle. Systematic *Chemical Abstracts* nomenclature, used in both the 9th and 10th Collective Indexes for the title compound and a selection of other compounds mentioned in the procedure, is provided in an appendix at the end of each preparation. Registry numbers, which are useful in computer searching and identification, are also provided in these appendixes. Whenever two names are concurrently in use and one name is the correct *Chemical Abstracts* name, that name is preferred.

SUBMISSION OF PREPARATIONS

Organic Syntheses welcomes and encourages submission of experimental procedures which lead to compounds of wide interest or which illustrate important new developments in methodology. The Editorial Board will consider proposals in outline format as shown below, and will request full experimental details for those proposals which are of sufficient interest. Submissions which are longer than three steps from commercial sources or from existing *Organic Syntheses* procedures will be accepted only in unusual circumstances.

Organic Syntheses Proposal Format

- 1) Authors
- 2) Title
- 3) Literature reference or enclose preprint if available.
- 4) Proposed sequence
- 5) Best current alternative(s)
- 6) a. Proposed scale, final product:
 - b. Overall yield:
 - c. Method of isolation and purification:
 - d. Purity of product (%):
 - e. How determined?
- 7) Any unusual apparatus or experimental technique:
- 8) Any hazards?
- 9) Source of starting material?
- 10) Utility of method or usefulness of product.

Submit to: Dr. Jeremiah P. Freeman, Secretary
Department of Chemistry
University of Notre Dame
Notre Dame, IN 46556

Proposals will be evaluated in outline form, again after submission of full experimental details and discussion, and, finally by checking experimental procedures. A form that details the preparation of a complete procedure (Notice to Submitters) may be obtained from the Secretary.

Additions, corrections, and improvements to the preparations previously published are welcomed; these should be directed to the Secretary. However, checking of such improvements will only be undertaken when new methodology is involved. Substantially improved procedures have been included in the Collective Volumes in place of a previously published procedure.

ACKNOWLEDGMENT

Organic Syntheses wishes to acknowledge the contributions of Hoffmann-La Roche, Inc., Merck & Co. and the Rohm and Haas Co. to the success of this enterprise through their support, in the form of time and expenses, of members of the Boards of Directors and Editors.

PREFACE

Like its predecessors, this volume contains checked and edited procedures dealing with important new synthetic methods or specific compounds holding potential interest for synthetic chemists. The compilation begins with three procedures detailing kinetic resolution by enzymatic means. Of these, the preparations of **(-)-(1R,2S)- and (+)-(1S,2R)-trans-2-PHENYLCYCLOHEXANOL** and **ETHYL (R)- and (S)-2-FLUOROHEXOATE** rely on lipase-catalyzed ester hydrolysis. The use of pig liver esterase for enantioselective saponification is nicely demonstrated in the case of **(1S,2S,3R)-3-HYDROXY-2-NITROCYCLOHEXYL ACETATE**. The next group of entries constitute a cluster of five stereocontrolled processes that have proven useful for constructing relative complex molecules. In the first, which targets **(4RS,4aRS,6RS,8aRS)-, (4S,4aS,6S,8aS)-, and (4R,4aR,6R,8aR)-4-METHOXYCARBONYL-1,1,6-TRIMETHYL-1,4,4a,5,6,7,8,8a-OCTAHYDRO-2,3-BENZOPYRONE**, an intramolecular Diels-Alder reaction is responsible for the diastereoselectivity. The stereoselective 1,4-functionalization of 1,3-dienes is exemplified by a two-step process leading to **cis- and trans-1-ACETOXY-4-(DICARBOMETHOXYMETHYL)-2-CYCLOHEXENE**. The effectiveness of a silyl hydride in providing a means for erythro-directed reduction of a β -keto amide is applied in a route to **ERYTHRO-1-(3-HYDROXY-2-METHYL-3-PHENYL-PROPANOYL)PIPERIDINE**. This is followed by an asymmetric synthesis based on a chiral bicyclic lactam leading to **(R)-4-ETHYL-4-ALLYL-2-CYCLOHEXEN-1-ONE**. The stereoselectivity with which acetoxy migration can operate to an adjacent radical center is reflected in the one-step reaction that gives rise to **1,3,4,6-TETRA-O-ACETYL-2-DEOXY- α -D-GLUCOPYRANOSE**.

The third set of procedures focuses on the vital role that organometallic reagents play in the transformation of functional groups. The first of the seven

illustrative examples provides details on the use of the Tebbe reagent for effecting the methylenation of esters. The two model systems are **1-PHENOXY-1-PHENYLETHENE** and **3,4-DIHYDRO-2-METHYLENE-2H-1-BENZOPYRAN**. In a similar vein, the efficacy with which mixed higher-order cyanocuprates can realize the opening of epoxides is demonstrated in the preparation of **1-BENZYL-4-PENTEN-2-OL**. Silicon-containing Grignard reagents are rapidly being developed as versatile and utilitarian reagents. In this context, the procedure to make **TRIMETHYL(2-METHYLENE-4-PHENYL-3-BUTENYL)SILANE** is a specific example of a one-step conversion of esters to allylsilanes. The readiness with which the nucleophilic hydroxymethylation of carbonyl compounds can be realized is illustrated by the formation of **1-(HYDROXYMETHYL)CYCLOHEXANOL**. A different use of Grignard chemistry is reflected in the hydromagnesiation of propargylic alcohols to afford **(E)-3-PENTYL-2-NONENE-1,4-DIOL**. New uses of lithium organometallics are illustrated in conjunction with in situ generation of acyllithium reagents from carbon monoxide as used in making **3-HYDROXY-2,2,3-TRIMETHYLOCTAN-4-ONE**, and with the propargylation of alkyl halides as employed for gaining access to **(E)-6,10-DIMETHYL-5,9-UNDECADIEN-1-YNE** and **(E)-7,11-DIMETHYL-6,10-DODECADIEN-2-YN-1-OL**.

The next cluster of seven procedures is grouped together in line with the long-standing *Organic Syntheses* tradition of providing preparations of starting materials that play an established role in important structural transformations and/or multistep syntheses. **N-FLUOROPYRIDINIUM TRIFLATE**, a versatile electrophilic fluorinating agent, is one such material. The companion preparations of **1-CHLORO-1-(TRICHLOROETHYL)CYCLOPROPANE** and **METHYL 2-CHLORO-2-CYCLOPROPYLIDENACETATE** describe reliable entry to useful three-membered ring building blocks. The next two procedures address the preparation of **(+)-(2R,8aS)-10-(CAMPHORYLSULFONYL)OXAZIRIDINE**, a selective, aprotic

oxidizing agent of considerable importance, and **(-)-D-2,10-CAMPHORSULTAM**, a chiral auxiliary that has found substantial use in asymmetric reactions of various types. A high-yielding, one-step route to highly functionalized sulfonyl acrylates is demonstrated by the preparation of **METHYL (Z)-3-(BENZENESULFONYL)-PROP-2-ENOATE**, a useful dienophile.

The next six procedures have a strong methodological bent. Thus, the pathway to **4-METHYLTRICYCLO[2.2.2.0^{3,5}]OCTANE-2,6-DIONE** is based on effective intramolecular oxidative coupling of a bisenolate. The preparation of **3,4-DIHYDRO-(2H)-AZULENONE** exemplifies the ability of a diazo ketone to undergo intramolecular cyclization onto an aromatic ring. A concise, four-component condensation forms the basis for a general unsaturated macrolide synthesis as illustrated for **8-PROPIONYL-(E)-5-NONENOLIDE**. The practicality of engaging keteniminium salts and chlorocyanoketene in efficient [2+2] cycloadditions is demonstrated by procedures leading to **3-HEXYLCYCLOBUTANONE** and **7-CHLORO-7-CYANOBI-CYCLO[4.2.0]OCTAN-8-ONE**. A catalytic means for oxidizing alcohols with oxammonium salts is employed for obtaining **(S)-(+)-2-METHYLBUTANAL**.

The volume concludes with three convenient procedures to make functionalized molecules having varied applications: **5,6-DIETHOXYBENZOFURAN-4,7-DIONE**, **9-n-BUTYL-1,2,3,4,5,6,7,8-OCTAHYDROACRIDIN-4-OL**, and **ETHYL 3,3-DIETHOXYPROPANOATE**.

The long-time standards of *Organic Syntheses* to provide for use by experimental organic chemists a collection of carefully checked, useful procedures have been extended to this volume thanks to the unstinting efforts of many individuals. Certainly, the members of the Boards of Editors and their students whose names are cited herein garner a large share of my appreciation for their time-consuming efforts in carrying out the rigorous protocols associated with checking the procedures. The

entire effort has been greatly facilitated by the impressive organizational skills of Professor Jeremiah P. Freeman, the Secretary to the Board. Finally, the production of the final product is largely attributed to his expertise and that of Dr. Theodore W. Greene, our Assistant Editor, whose painstaking efforts with the textual material provide the very attractive and readable text that is before you.

Columbus, Ohio

Leo A. Paquette

March 1990

MAX TISHLER

October 30, 1906 - March 17, 1989

Max Tishler combined, to an exceptional degree, excellence in two seemingly diverse areas. He was a giant in advanced and sophisticated medicinal chemistry research and an administrator with a remarkably inspirational gift for teaching and academic leadership. On the one hand, Tishler pioneered the round-the-clock system for pressure research at Merck. Later, he became the quintessential undergraduate and graduate mentor at Wesleyan University. A distinguished career in industry culminated as President of Merck, Sharpe & Dohme Research Laboratories. Tishler was Editor-in-Chief of Volume 39 of *Organic Syntheses*, which was published in 1959.

Max Tishler was born in Boston on October 30, 1906. He received the B.S. in 1928 from Tufts College, and the M.A. from Harvard in 1933 while working part-time as a pharmacist. The Ph.D. degree was awarded in 1934 by Harvard. After scientific collaboration with E. P. Kohler and J. B. Conant, he joined Merck & Company, Inc. Research Laboratories in 1937. After retiring from Merck, Dr. Tishler was appointed Professor of Chemistry at Wesleyan University in Middletown, Connecticut (1970 - 1972); University Professor of Sciences (1972 - 1975); and Emeritus (1975 - 1989).

Dr. Tishler published more than 100 scientific papers and is cited as an inventor on more than 100 United States patents. A partial list of research contributions include development of processes for the commercial production of vitamin B6, vitamin K, vitamin E, penicillin, streptomycin, and cortisone.

Dr. Tishler was very active in the American Chemical Society, serving for many years on the Board of Directors and as President in 1972. He received the Priestley Medal of the ACS in 1970. He was a member of the National Academy of Sciences. Tishler received an honorary Sc.D. from Tufts University in 1956 and a D.Eng. from Stevens Institute of Technology in 1966. In 1987, he received the National Medal of Science.

An anecdote illustrates Tishler's drive. The total synthesis of cortisone, as devised by Lewis Sarrett, comprised approximately 30 steps and required weeks of intense and painstaking effort. Max was in charge of the first commercial production of cortisone in the pilot plant. One of the final steps is the isomerisation of a double bond into conjugation with the 3-ketone function with the formation of a 2,4-dinitrophenylhydrazone, causing the development of a brilliant, scarlet color. Tishler was inspecting the first production run. To his horror, he spotted a bright-red liquid leaking near the vessel. "I hope that's blood!", he exclaimed. Actually, Max was very concerned for individuals, beneath a rather formidable exterior.

A story of my contacts with Max Tishler after my Merck days is worth recounting. My MIT group was busily preparing 100-gram quantities of penicillamine for use in our penicillin synthesis program. A Professor of Chemical Medicine at Harvard, Dr. Charles Davidson, and a British medical colleague requested a sample of penicillamine for their experimental program relating to sequestering copper ion. About one year later, my MIT telephone started jumping off the hook, frantic telegrams arrived, and one anxious visitor was at my door. It seems that an article had appeared in the British medical journal, *Lancet*, reporting that penicillamine was very helpful in the symptomatic treatment of Wilson's Syndrome, a disorder characterized by the accumulation of cupric ion in the brain. In a footnote, "Prof. John C. Sheehan of MIT" was credited with furnishing the penicillamine. The visitor at my office was offering to pay almost any price since his son suffered from the disease. I told him that not only could I not sell the compound, but I could not even give any away, even to his physician, since it was not approved by the FDA.

I telephoned Max Tishler, outlined the situation, and he said he would call back that afternoon. Max contacted the Merck Medical Department, who stated that Wilson's Syndrome was a rare condition affecting only about 50 to 100 patients a year, and was terminal. However, Max was able to launch a crash program to prepare penicillamine at Merck and get quick FDA approval under the "orphan disease" category, in spite of the unpromising commercial outlook.

He is survived by his wife, Elizabeth (Betty) Tishler (married in 1934) and two sons -- Peter Vermeer Tishler and Carl Lewis Tishler.

June 4, 1990

John C. Sheehan

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